CONTRIBUTIONS TO EMBRYOLOGY

VOLUME II, NOS. 2, 3, 4, 5, 6

WASHINGTON, D. C.
PUBLISHED BY THE CARNEGIE INSTITUTION OF WASHINGTON
1915

CARNEGIE INSTITUTION OF WASHINGTON
Publication No. 222

9032

PRESS OF GIBSON BROTHERS
WASHINGTON, D. C.

CONTENTS.

PAGES.

No. 2. Description of two young twin human embryos with 17–19 paired somites. By James Crawford Watt (7 text figures and 4 plates) 5–44

3. An anomaly of the thoracic duct with a bearing on the embryology of the lymphatic system. By Eliot R. Clark (3 figures) 45–54

4. Fields, graphs, and other data on fetal growth. By A. W. Meyer (15 figures) .. 55–68

5. The corpus luteum of pregnancy, as it is in swine. By George W. Corner (3 plates) 69–94

6. Transitory cavities in the corpus striatum of the human embryo. By Charles R. Essick (3 plates) 95–108

CONTRIBUTIONS TO EMBRYOLOGY, NO. 2.

DESCRIPTION OF TWO YOUNG TWIN HUMAN EMBRYOS WITH 17-19 PAIRED SOMITES.

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With 7 text figures and 4 plates.

CONTENTS.

	PAGE.
Introduction	7
Preservation and Mounting	7
Methods of Study	7
Age of the Embryos	8
External Appearance	9
Amnion	11
Chorion	12
Integument and Epithelial Thickenings	12
Mesodermic Somites	13
The Notochord	17
Alimentary System	20
Circulatory System	25
Urinogenital System	30
Septum Transversum and Cœlom	35
Sense Organs	36
Nervous System	37
Conclusion	42
Bibliography	43
List of Abbreviations used in Illustrations	44

DESCRIPTION OF TWO YOUNG TWIN HUMAN EMBRYOS WITH 17-19 PAIRED SOMITES.

By James Crawford Watt.

INTRODUCTION.

The human embryos herein described are Embryos V and VI in the private collection of Professor J. Playfair McMurrich. They were sent from Denver, Colorado, in 1908, by Dr. Mary Hawes, who found them discharged by the uterus of a patient who had called her during a miscarriage. They are specially valuable, as they occur midway in the interval between embryos of 13–14 paired somites and those of 22–23 paired somites described in Keibel and Elze's Normentafel (1908). For the filling in of this large interval there has hitherto been a great scarcity of material, so these embryos are described in detail, to serve as an example of at least one stage in bridging the gap.

The following facts are recorded concerning these embryos. The father was a German Jew, 31 years old, tailor by occupation, and affected by tuberculosis for the last 5 years. The mother was a German Jewess, 30 years old, robust and healthy, and had borne four children previously, all living, the youngest being three years old and delicate in health. Previous to this abortion the mother had experienced no trouble during her pregnancies.

As regards this abortion, the last menstruation began on December 3, 1907, the flow being perfectly normal and lasting three days. Coitus first occurred after this on December 20, and the next menstruation did not appear on the expected date. Three days later, however, on January 3, 1908, there occurred a slight bloody flow, followed by other similar ones on the 11th, 12th, and 13th of the month, the intervals between these discharges being entirely free. On the morning of January 14 there were three severe pains, followed in the afternoon by hemorrhage, and ending in the night by the expulsion of twin sacs from the uterus.

PRESERVATION AND MOUNTING.

These sacs and their contents were, immediately after their extrusion from the uterus, placed in 10 per cent formalin solution, followed by 70, 80, and 95 per cent alcohol. The sacs were then cut away, except where the embryos were attached, and measurements and drawings of each embryo were made. Each was then cut transversely into serial sections 10μ thick, which were stained on the slides with hemalum followed by erythrosin. Both embryos, upon examination, appeared very similar in all features, so Embryo VI, which was somewhat the clearer of the two, was selected for the most thorough study, the results being supplemented by the findings in Embryo V.

METHODS OF STUDY.

By the aid of the camera lucida each section was carefully drawn at a magnification of 200 diameters and from these drawings, following Born's wax-plate method of reconstruction, a model of the embryo was made. As there were 335 sections in the embryo, each 10μ thick, the model measured 670 mm. or 27 inches long, each plate being 2 mm. thick. The left side of the model shows the external appearance of the embryo, while on the right side the skin and mesenchyme were not reconstructed, so giving a view of the internal structure.

The model was also left in blocks of varying thickness, so that the structures not seen from the outside might be followed, and it is possible thus to see the main points of the nervous, alimentary, circulatory, and nephrogenic systems, and the mesodermic somites.

For closer study, and also for use in illustrating this paper, special wax models were made of the brain, heart, pharynx, and cloaca. Graphic reconstructions were made of the nephrogenic system from the dorsal, medial, and lateral surfaces, using His's method of plotting points on squared paper, and also a new and very instructive method described by Buist (1913), known as contour reconstruction, in which an element of perspective is introduced. Owing to the nature of this latter method there is, however, a considerable oblique distortion which must be taken into account in interpreting the results.

In addition to the above, the sections were gone over many times under the microscope and the results of all methods have been correlated and incorporated as one in this paper. The supplementary results appended in the description of each part, concerning Embryo V, were all obtained by microscopic study of the sections and comparison of them with sections of the same region in its twin, Embryo VI.

AGE OF THE EMBRYOS.

From the data given above it is difficult to determine accurately the age of these embryos. Counting from the first coition after the last menstrual period, which gives the earliest possible date of conception, December 20, to the last possible day of the embryo's life, January 13, we get 24 days as the greatest age, and if conception were later and death earlier the age will be several days less. The total length of Embryo VI, determined from the serial sections, is 3.35 mm. and by applying Mall's (1903) rule that the age of the embryo in days is equal to the square root of 100 times the length in millimeters, we get 18 days as the result. His (1880) estimates embryos of 3 to 4.5 mm. given length as being $2\frac{1}{2}$ to 3 weeks old, and the ages for most embryos since described are based on these estimates. It will be seen that the age of these embryos agrees with the estimates of His and Mall fairly well.

On the other hand, Eternod (1895) states the age of an early embryo described by him, which measured only 1.3 mm., as 21 days, and he had very definite data upon which to figure. The embryo described here is 3.35 mm. long, and of a degree of development far advanced beyond Eternod's; yet, counting from the coition of December 20, it must be accepted as 24 days or less in age, that is, at the most, only 3 days older than Eternod's. The results are entirely contradictory as they stand, but it is quite possible that Embryo VI is really much older than appears from the above facts, and if so, they will entirely agree. It is a well-known fact that spermatozoa can live for weeks in the Fallopian tubes, which practically act as receptacula seminis, and this embryo may be the product of fertilization of an ovum from about the last menstruation by a spermatozoon from a coitus previous to this period, and which would have been in the tube some days. If fertilization occurred immediately after menstruation the embryo would be 5 weeks old; if during or just before the flow, another half week would be added to the age. It would be quite possible for the ovum to be fertilized just before menstruation and not be lost, as it would probably not leave the tube and enter the uterus before the flow was over. Menstruation during early pregnancy also is not unknown. If 5 weeks be the correct age it corresponds accurately with figures given by Professor McMurrich (1913) in the last edition of "The Development of the Human Body." Taking the ages of a few embryos where very exact information is available, he says the ages of all early embryos have evidently been underestimated; an

embryo 2 to 3 mm. in length belongs to the fourth week, one 5 to 6 mm. in length to the end of the fifth, so that one 3 to 4 mm. long should belong to the early part of the fifth week.

In Keibel and Mall's Human Embryology (1912) it is also stated by Mall that the ages of early human embryos have all been underestimated previously by about 10 days, so that adding this amount to the results arrived at by comparing this embryo with His's results, would give almost 5 weeks as its age. The range of variation in the age of this embryo lies thus between 18 days on one hand and 30 to 35 on the other, according to the authority chosen, and it becomes impossible to state which of two coitions is responsible for fertilization, even though they are separated by an interval of 3 weeks and have a menstrual period intervening.

The length of Embryo V throws no light on this question. Indeed, at first glance, it seems to offer a contradiction. This embryo measures 2.75 mm., according to the serial sections, being 0.60 mm. shorter than its twin. It is of exactly the same stage of development, however, and the discrepancy in length is accounted for by the presence of a very deep concave dorsal bend, while the corresponding bend in Embryo VI is very shallow, measurements thus including almost the whole extent of the back in the latter but not in the former. Embryo V is almost identical in development with Embryo VI, but is not actually an identical twin, as the two embryos are the products of two separate ova, as shown by the presence of a separate complete sac for each.

EXTERNAL APPEARANCE.

In external appearance Embryo VI resembles most closely embryo 6 (figs. Vr and Vv) in Keibel and Elze's Normentafel (1908). This is embryo Pfannenstiel III, described by Low. There is also a close resemblance shown to figure 4 of His's Normentafeln (1880). The head of the embryo is rounded and small, and shows on each side a slight swelling marking the position of the optic vesicles. Between these is the anterior neuropore, still a fairly wide opening. The head is sharply flexed on the long axis of the body, forming a well-marked cephalic bend, and lies immediately in front of the very prominent, bulging heart region. Between these two parts of the body lies a wide slit, which narrows rapidly as it passes inwards and forms the primitive mouth cavity or stomodæum. Between it and the pharynx is a distinct quadrangular membrane, the buccopharyngeal membrane, which is still complete, except for 3 small, circular perforations, the membrane evidently just beginning to rupture. In embryo Pfannenstiel III, of 14 somites, described by Low (1908), it is still complete, and also in embryo Bulle, of 14 somites, described by Kollmann (1890). In the embryo with 23 somites described by Peter Thompson (1907) it has just torn completely, so that this embryo of 18–19 somites, with perforations just beginning, fits exactly into the series.

For two-fifths of its entire length the embryo lies spread out wide open over a large yolk sac, and is much flattened dorsoventrally. The yolk sac, at its junction with the body of the embryo, shows no constriction whatever laterally, but only in front and behind, so that the yolk stalk apparently is only beginning to be differentiated. Over the posterior part of the yolk sac there is a shallow but distinct concave dorsal bend in the body of the embryo, and immediately posterior to this the body is rounded and bulging and exhibits a convex sacral bend as it runs rapidly to its termination in a small, blunt, conical tail. The wide yolk stalk, concave bend, and short, blunt, posterior portion of the body are almost identical in appearance with those of the embryo described by Low (1908). Other similarities are to be seen in an appreciable interval between the yolk stalk and belly stalk, and in

the exocœlom being very large and communicating with the endocœlom by a wide gap extending along the side of the embryo, beginning immediately behind the heart and measuring about half the total length of the embryo.

It is interesting to note that up to the 14-somite stage most early embryos exhibit the concave dorsal bend, but beyond this is a gap up to the embryo of 23 somites described by Thompson (1907) and two, of 22 and 23 respectively, described by Van den Broek (1911). None of these latter show the bend, but instead a rounded, convex back. The twin embryos here described occur in the middle of this interval, with 18–19 somites, and both exhibit this concave bend. The flexure is regarded usually as an artifact and is probably produced as follows: The posterior end of the body is round and solid, and firmly attached to the belly stalk. The anterior end is large, round, and heavy with the immense relative size of brain, pharynx, and heart. The middle connecting part of the body between these two heavy ends is fairly thin and therefore weak, and has the yolk sac suspended ventrally and dragging upon it. In handling the embryo for fixing and embedding, there must be dragging of yolk sac and belly stalk upon the body when the embryo is moved, and this pull in one direction, with the heavy ends sagging in the opposite, practically breaks the back, bending it severely. This appearance is of value, then, only as an indication of the strength of the middle region of the back, disappearing when this part of the body has become sufficiently strong, and because of the relative diminution in size of the umbilical opening and the passage of the amnion out around the whole umbilical cord, binding belly stalk and yolk stalk together and thus strengthening the middle region of the body.

Coming from the ventral surface of the body, just behind the yolk sac, is the large belly stalk, flattened on its dorsal surface but rounded on the others. It has a course of 1 millimeter from embryo to chorion, being thus about one-third the length of the embryo. The embryo lies somewhat twisted upon its long axis, the head to the right over the heart, the tail to the left over the belly stalk. The side to which the tail turns in the spiral seems to be variable, being to the left here and in embryos described by Wallin (1913), Low (1908), and Mrs. Gage (1905), but to the right in cases recorded by Bremer (1906), Van den Broek (1911), and Ingalls (1907). Mall (1891) describes a case going to the left and says that the bend to the right is more usual.

The heart forms a very large, prominent bulging occupying the whole ventral body wall between yolk sac and stomodæum. It agrees with that of the Peter Thompson and Van den Broek embryos in that it projects much farther forward on the right side than on the left. It is interesting to note that in the Ingalls (1907) embryo, 4.9 mm. in length, the heart lies mostly to the left. The position of the chambers of the heart is indicated externally by shallow grooves on the surface, bounding gently rounded prominences overlying the chambers.

Starting at the sides of the stomodæum, and passing on each side caudally, is a well-marked groove, or sulcus, which marks off the heart region ventrally from the rest of the body lying dorsal to it. This sulcus extends back to meet the line of reflection of the amnion, where it is lost. Just caudad, and also somewhat dorsal to the stomodæum, is a shallow groove, or depression, running dorsoventrally, its lower end meeting the sulcus bounding the heart. This marks the position of the first gill cleft. A short distance directly caudad, and lying parallel to the first, is the depression of the second gill cleft, about equal in extent but shallower than the first. It also reaches ventrally the limiting sulcus of the heart. Immediately dorsal to the second gill cleft lies the otocyst, a deep, oval depression of the ectoderm, still opening widely to the outside. In Low's embryo,

with 13–14 somites, 3 gill clefts are visible externally, while in this embryo, with 18–19 somites, there are only 2. Only 2 are to be seen externally in Janošik's (1887) embryo of 3 mm. and Wallin's (1913) of 2.3 mm. Again, in the 2 described by Van den Broek, with 22 and 23, and 1 by Thompson with 23 somites, there are 3 clefts, the same number as in Low's embryo, which thus seems to show a precocious formation of the third cleft. For if 3 were normally present at the 14-somite stage, at a stage with 9 somites increase we would expect the appearance of a fourth cleft, which is not found until embryos are reached such as Bremer's (4 mm. in length), Mrs. Gage's (4.3 mm. long with 28 somites), or Ingalls's (4.9 mm. long with 35 somites).

As in all embryos described in the early stages, this embryo does not show externally the position of the anterior mesodermic somites, but in the region of the concave dorsal bend and the rump they are indicated by noticeable protuberances.

There is no indication whatever of the limbs.

The nervous system is still open to the exterior in two places, the anterior and posterior neuropores. The anterior neuropore is a wide opening situated in a shallow depression at the extreme anterior aspect of the flexed head, and lies directly between the optic vesicles. The posterior neuropore begins in the rump, where the roof of the neural canal ends and the canal opens as a deep gutter, whose walls gradually decrease until the gutter form is lost and it forms only a flattened medullary plate extending out on the tail.

It will be seen, from the above description, that this embryo, while situated exactly half way between two well-known stages of development, resembles embryos younger than itself very much more than older ones, and although much greater in size, in many respects does not seem to be any further developed than the younger ones. The main differences from the above description of Embryo VI, which are shown by Embryo V, are in the possession by the latter of a very deep concave bend in the back, a yolk stalk that is definitely constricted at the sides as well as before and behind, and in the fact that the long axis of the embryo practically forms a straight line and not a spiral. The belly stalk passes directly backward under the tail.

THE AMNION.

There is a well-developed, completely closed amniotic cavity. The amnion itself is formed of two closely applied but quite distinct layers of flattened cells, the nuclei appearing at scattered intervals and forming swellings in the cell layer where they lie. The amniotic cavity is fairly extensive and an idea of it can best be given by describing the line of reflection of the amnion from the body of the embryo. The whole of the head and the anterior half of the heart region are placed entirely within the cavity, the most anterior point of the origin of the amnion being about half way back on the ventral surface of the bulging heart region, in a line convex forward. From here it inclines obliquely upward on each side of the heart, until it crosses the septum transversum, where it immediately changes direction and runs directly caudad on the lateral body wall. The body in this region is so flattened dorsoventrally that only the upper surface is in the amniotic cavity. On reaching the region of the origin of the belly stalk, the line of reflection again crosses the rounded body wall obliquely, this time toward the ventral surface, and passes off on the belly stalk, from the borders of the flattened dorsal surface of which it is reflected right out to the chorion. The whole of that portion of the embryo posterior to the belly stalk thus projects, like the head, into the amniotic cavity, and a narrow, tapering, or funnel-shaped prolongation of the cavity is continued over the upper surface of the belly stalk, its apex being in contact with the chorion.

The above description shows this reflection of the amnion in this embryo to be essentially similar to that given by Low for embryo Pfannenstiel III. The embryo described by Thompson (1907) shows the nearest stage described in advance of this. Here the whole heart region projects into the cavity, the amnion being reflected from the ventral body wall on the line of the septum transversum. The amnion is also shown beginning to pass out over the yolk stalk, so that the large aperture of the umbilical vesicle of previous stages here begins to be constricted. Posteriorly the amnion only covers the narrow, dorsal aspect of the belly stalk, and still exhibits the narrow, conical prolongation of the cavity.

There are no differences to be noted regarding the amnion of Embryo V.

THE CHORION.

The chorion agrees in every respect with the description given of other embryos. It is from 0.09 to 0.18 mm. thick and the villi arising from it are 0.17 to 0.25 mm. in diameter and 1.0 mm. to 1.6 mm. in length. These measurements are not very much greater than those given by Dandy (1910) for an embryo about 2 mm. long, with only 7 pairs of somites. As most of the chorion had been removed before the embryo was received, it can not be stated whether the whole sac was equally covered by villi, or not.

The inner surface of the chorion and the interior of the villi are formed of loose mesenchyme consisting of branching spindle and stellate cells. The nuclei of the cells are oval and vesicular, the protoplasm stains very lightly and forms only a thin covering over the nucleus and the numerous fine branching processes. The intercellular tissue spaces are large, and contain a clear jelly-like substance. Numerous large blood-vessels are found everywhere in this tissue in the chorion and its villi.

The outer surface of the chorion and villi is formed of two epithelial layers of cells. The inner layer, the Langhans cells, lying next the mesenchyme, have moderately staining nuclei and protoplasm. In sections vertical to the plane of the cell layer, the cells appear cubical in form and are very little deeper than is just sufficient to contain the large round vesicular nuclei. Cell boundaries are evident and distinct. In sections parallel to the surface of this layer the cells appear large and polygonal in outline, the majority being 5-sided. The outer layer is a syncytium formed of a densely stained, granular protoplasm containing deeply stained, flattened, oval nuclei which lie with their long axis parallel to the surface of the layer. This layer is thinner than the Langhans layer and contains fewer nuclei, and I find, contrary to Dandy (1910), that the nuclei of the Langhans cells are much larger than the nuclei of the syncytium.

INTEGUMENT AND EPITHELIAL THICKENINGS.

The ectoderm is nowhere separated from the nervous system except over that part of the brain tube between the anterior neuropore and the buccopharyngeal membrane. At the anterior and posterior neuropores it is fused with the wall of the nervous system, and everywhere else is connected by the neural crest to the mid-dorsal line of the neural tube. The ectoderm is in general a 1-celled layer, but exhibits thickenings in certain definite regions. In the dorsal portions of the body it forms a single layer of flattened cells and presents a similar appearance ventrally over the heart region and at the sides of the body close to the line of attachment of the amnion. Over the mesodermic somites its cells are cubical, and this condition is maintained even in front of the somites, far up into the head. Over the gill arches the ectoderm is much thickened and is 2-layered. These conditions are exactly similar to those described and illustrated by Ingalls (1907) for an embryo

4.9 mm. long. He found thickenings over 4 arches, 4 gill pouches being present in his embryo; only 2 gill pouches are to be found here, yet thickenings are present over 3 arches.

There is as yet no trace whatever of the formation of the lens of the eye or of the olfactory placode. In the condition of the cloacal membrane this embryo agrees with that described by Mrs. Gage (1905), who found the anal plate thickened in an embryo of 28 somites. Ingalls found it very thin and in places almost unrecognizable in one of 35 somites. In the present embryo, at the 18–19 somite stage, it is quite thickened and differs in appearance from the adjacent ectoderm. The endoderm, as in the case of the two embryos cited above, is in contact with and apparently fused to the ectoderm, and is also thickened.

MESODERMIC SOMITES.

These embryos stand mid-way between stages 5 and 6 in Keibel and Elze's Normentafel, where the embryos possess 13–14 somites, and stages 7 and 8, of 23 paired somites. Embryo VI possesses 18–19 paired somites. There are 18 fully formed and distinct pairs of somites and a nineteenth pair is well formed but not yet cut off from the unsegmented mesoderm behind (text fig. 3). The first somite lies at the level of the posterior portion of the heart. It is a peculiar coincidence that the last somite occurs exactly at the level of the opening of the medullary canal into the medullary groove at the posterior neuropore. This also is the exact level of the fusion posteriorly of the somatopleure and splanchnopleure, cutting off ventral communication between the endocœlom and the exocœlom.

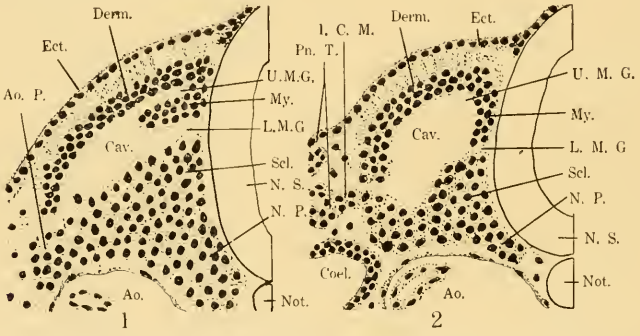
The general shape of the somites is that of a triangular prism with rounded anterior and posterior ends, and a ventral, a medial, and a dorsolateral wall. The more posterior somites are more quadrangular than prismatic. The fourth, fifth, and sixth somites lie somewhat obliquely to the long axis of the body, and between their posterior ends and the medullary canal the anterior ends of the succeeding somites are inserted. The eleventh to fifteenth pairs of somites inclusive lie in the region of the concave dorsal bend and the posterior portion of the dorsolateral surface of each of these is overlapped by the anterior end of the next.

In describing the various parts of the somite, dermatome is the term used to denote the flat plate forming the whole dorsolateral surface, myotome denotes the dorsal half of the medial surface, and sclerotome the lower half of the medial surface, the whole of the ventral surface, and the core of the somite.

The first somite is very small. Its ventromedial portion is of somewhat looser, more irregular tissue than the rest of the somite and suggests the beginning differentiation of the sclerotome. There is a distinct solid core fused with this and almost obliterating the cavity of the somite, which appears only as a narrow slit. The dermatome and myotome are differentiated from each other only by the presence of the upper myotomic groove. The somite lies surrounded on all sides by dense mesenchyme with which it fuses anteriorly, so that there is no distinct anterior end to it. This fusion of mesenchyme and first somite is exactly similar to the condition described for the chick by Williams (1910), who found in a series of embryos that this somite is the first formed both in time and position, but develops extremely slowly compared to the others. The second somite shows the greatest degree of development of the whole series and each succeeding somite shows a retrogressive decrease in the degree to which it has attained. Each somite shows not only differences in degree of development but also individual differences in shape and appearance, so that no two exactly correspond. The second somite in this embryo shows almost exactly the

same stage of development as the corresponding somite of a chick embryo of the 18-somite stage described by Williams. The dermatome is a flattened plate underlying the ectoderm and formed of the whole dorsolateral wall. The myotome is flexed under the dermatome medially and extends out about half the extent of the dermatome laterally, lying in contact with the latter and including between itself and the latter a small cut-off portion of the general cavity of the somite in the dorsomedial angle.

There is a deep cleft, named by Williams the lower myotomic groove, separating the myotome from the sclerotome below it. The sclerotome is formed of a mass of looser cells forming the ventromedial and ventral part of the wall of the somite, and from the ventral surface of this two long, curved, plate-like processes pass off. The inner one, the notochordal process, passes medially between the medullary canal and the dorsal aorta to the side of the notochord. The lateral one, the aortic process, passes ventrally around the lateral surface of the aorta toward the wall of the pharynx, its ventral end being indistinct and hard to differentiate from the surrounding mesoderm. The notochordal process arises from the whole extent of the ventral surface of the sclerotome, but the aortic process comes only from the anterior two-thirds, and there is a distinct interval between it and the next succeeding aortic process, except in the case of the second and third somites, in which these processes are fused. The cavity of this somite is distinct and irregular and is not very large. The core is fused with the sclerotome and is indistinct.



1. Transverse section through the middle of the fifth mesodermic somite on the right side in Embryo VI. Drawn with camera lucida. Magnification × 270.
2. Transverse section through the middle of the twelfth mesodermic somite on the right side in Embryo VI. Drawn with camera lucida. Magnification × 270.

For list of abbreviations see page 40.

The appearance of each succeeding somite differs somewhat from the description given above for the second, the main difference being that proceeding caudad there is a retrogression in the amount of differentiation of the parts of the somite. The size of the somitic cavity increases greatly and is very large from the eighth to sixteenth somites and then decreases rapidly and is merely a slit in the nineteenth. There is apparently connection of some of these cavities with the cœlom.

Only the myotomes of the second to fifth somites (text fig. 1) inclusive are flexed sufficiently to lie in contact with the under surface of the dermatome and so cut off a small portion of the somitic cavity. Proceeding caudally, they become less and less strongly flexed and the groove on the inner surface at the dorsal angle of the somite, named by

Williams the upper myotomic groove, becomes more and more a rounded angle (text fig. 2), until beyond the thirteenth somite it is impossible to state that it is present. The lower myotomic groove is distinct as far back as the thirteenth segment, but after that it is hardly recognizable, although the distinction between myotome and sclerotome is clearly shown by the character and arrangement of the cells and by a slight chink, or split, in the wall at the point where this groove will develop.

The sclerotome is present in every somite, though in the first and last it is only distinguishable from the rest of the somite by the slightly looser arrangement of the tissue and more irregular outline. These two somites also are the only two possessing a well-marked core, which in each case fills up and almost obliterates the somitic cavity. There is evidence of a core in the other somites, but it has evidently fused with the sclerotome and passed ventrally with the latter, largely losing its identity.

The notochordal process of the sclerotome (text figs. 1 and 2) is present in all segments from the second to the sixteenth, and in this series shows a marked decrease in development in each segment proceeding caudad. It comes off the whole ventral extent of the sclerotome and curves inward under the medullary canal to the notochord, but nowhere does it surround the latter, merely coming laterally into contact with it. As far back as the seventh segment the notochordal processes have fused and obliterated the lower portion of the intersegmental clefts originally present between them. These clefts still persist between every two processes posterior to this point.

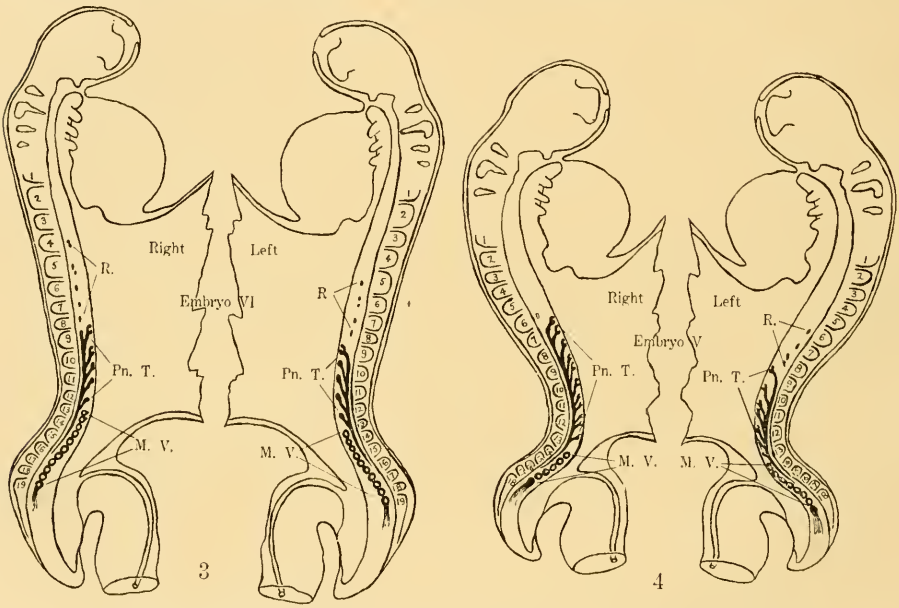
The aortic process is present in each sclerotome (text fig. 1) as far back as the thirteenth, where it finally disappears. No two of these fuse or come into contact except in somites 2 and 3, and they are separated by intervals considerably larger than the intersegmental clefts, as they are developed, not from the whole ventral extent of the sclerotome, but only from the anterior three-fourths to two-thirds of this extent. Beyond the thirteenth segment there is no evidence whatever of the aortic process, which is thus a slightly later development of the sclerotome than is the notochordal process.

From the ninth segment to the end, the nephrogenic tissue, the intermediate cell mass, is connected to the lateral angles of the somites. In some instances it appears as if separation were just commencing and the wall of the somite is broken at this point and the cavity is open. The attachment to the somite is on a line between dermatome and sclerotome (text fig. 2).

There is an intersegmental cleft between every two somites, but none cutting off the nineteenth posteriorly. This nineteenth somite has a dermomyotome, a core, a sclerotome, and a small cavity, and is almost the equal in size of the somite just ahead of it, but is still fused posteriorly with the unsegmented mesoderm. In each intersegmental cleft is a small amount of loose mesenchyme, which is also seen burrowing around the anterior and posterior rounded ends of a few of the most anterior somites, working between them and the ectoderm. In these somites mesenchyme is also burrowing in from the lateral edge between the dermatome and the ectoderm. No mesenchyme is found between the medullary canal and any somite (except the first, which is incomplete and fused with mesoderm anteriorly), and each somite lies in contact medially with the wall of the medullary canal. Also, no mesenchyme is found, except as stated above, between the dermatomes and the ectoderm.

The dermatomes and myotomes are epithelial in nature. The cell nuclei are large, round, and vesicular, and in the dermatomes are crowded toward the wall of the cavity of the somite, leaving only the cell bodies to form the peripheral portion of the layer. The

ends of the cell bodies anastomose freely immediately beneath the ectoderm, but no external limiting membrane is to be distinguished, such as Bardeen (1900) has described in the pig. Williams (1910) in the chick finds the dermatomes exactly similar to the above and is also unable to demonstrate any external limiting membrane. Regarding Bardeen's contention that the dermatome does not form the cutis layer of the skin and really gives rise to muscle tissue only, as he found in the pig, little light can be obtained here. It is significant, however, and partly confirmatory of Bardeen's results, that in the most advanced segments the dermatomes are beginning to recede from contact with the ectoderm and loose mesenchyme in finding its way between the two at the edges of the dermatome. It is to be expected that this loose mesenchymatous tissue would develop *in situ* into the cutis layer later on, and, if so, the so-called dermatome would be really all myotome.



3. Graphic reconstruction to show the position and relations of the mesodermic somites and the nephrogenic system in Embryo VI.
4. Graphic reconstruction to show the position and relations of the mesodermic somites and nephrogenic system in Embryo V.
The numbers refer to the mesodermic somites. For abbreviations see page 40.

The undifferentiated mesoderm back of the somites is very solid and condensed, and lies in contact with the medullary canal and the ectoderm, no loose tissue whatever intervening. The intermediate cell mass at first is cut off from it, forming the nephrogenic cord, but very soon is seen to be fused with the somitic plate on one hand and the splanchnic and somatic mesoderm on the other. This common mass of mesoderm passes into the tail to fuse with the primitive streak.

For some distance caudad of the last somite, a peculiar narrow process passes off ventrally from the undifferentiated mesoderm on each side and, running between the dorsal aorta and the medullary groove, comes into contact with the notochord. It is very sug-

gestive of a precocious formation of the notochordal process of the sclerotome in somites yet to be differentiated, and is perfectly similar in shape and position with the notochordal processes already formed.

Embryo V is almost identical with Embryo VI. There are 17 pairs of somites, complete and distinct, and an eighteenth pair is to be seen forming in the undifferentiated mesoderm. The aortic processes of the second, third, and fourth somites, and the notochordal processes also of the same, have fused into common masses. Back of this, all processes remain separate from those preceding and succeeding. There is thus fusion of one more aortic process, but of three less notochordal processes than in its twin. The aortic processes end in the twelfth segment, there being thus one less than in Embryo VI.

THE NOTOCHORD.

The notochord extends continuously from just behind the hypophysis cerebri to the caudal region (plate 1) and is clearly distinguishable throughout the whole course, although varying greatly in its degree of development in different regions. It will be necessary, in order to obtain a proper conception of it, to trace its course and describe its appearance in the various regions.

The notochord first appears immediately posterior to the hypophysis and is here formed by a heaping up of cells around a median groove on the dorsal wall of the foregut. Bremer, Broman, Van den Broek, and Ingalls all describe it as beginning immediately behind the hypophysis, just as is found here. Peter Thompson places it at the flexure between midbrain and forebrain, and Janošik just under the midbrain. Evidently back of the hypophysis is the normal point. In this embryo this point is the extreme cephalic end of the dorsal wall of the gut (plate 2, fig. 1). The groove disappears by the time the region of the first gill arch is reached (plate 2, fig. 2), but the heaping up of cells persists and is somewhat higher and narrower than anteriorly. Over the region of the second gill cleft the median groove again appears in the roof of the pharynx and the notochord is here seen in its most rudimentary condition in this embryo (plate 2, fig. 3), being formed merely of a flattened double layer of endodermal cells lining the groove. Mrs. Gage (1906) has shown that long after the notochord has separated from the endoderm elsewhere it retains connection with it in this region, both in man and the pig, and Huber (1912) has proved that it is in this region that the pharyngeal bursa is developed, due to the evagination of the wall of the pharynx by the pull of the notochord attached here. Neither of the above described the condition in embryos younger than stages showing complete formation of the rod-like notochord, but it is interesting to note that although the notochord is not yet separated from the endoderm in any of this anterior region, yet this point, corresponding to the region where the pharyngeal bursa later appears, can be determined as the place of the very least development of the notochord, and therefore the place where separation will last occur, so giving the conditions described by Huber and Mrs. Gage. Proceeding backward, the notochord becomes thicker, more heaped up, and gradually assumes a spherical form on section, and forms a round rod (plate 2, fig. 4) merely lying in contact with the endoderm. Over the anterior portion of the yolk sac this rod begins to separate from the endoderm and for a short interval mesoderm passes between the two, and then the two dorsal aortæ, which have been rapidly approaching each other, fuse immediately over the gut and directly beneath the notochord (plate 2, fig. 5). Over the posterior portion of the yolk sac the aorta again becomes paired and the notochord immediately sinks to come

into contact with the endoderm, with which it is connected by a narrow neck of cells (plate 2, fig. 6). It is in this region that the notochord attains its largest diameter.

In the dorsal wall of the hindgut a median longitudinal groove now develops along the line of attachment of the neck of cells from the notochord and coincidently with the deepening of this groove the notochord loses its spherical condition, becomes elongated dorsoventrally and compressed laterally into a flask shape (plate 2, figs. 7 and 8), and then passes rapidly into a condition similar to that at the anterior end, forming a heap of cells surrounding the groove. In descriptions of embryos in these early stages, I have found no mention of any condition of delayed development such as this. The rod-like form, once attained behind the pharyngeal region, has been retained to the caudal termination. This condition is small in extent, however, and by gradual transition the notochord is again found spherical in section (plate 2, fig. 9) at the level of origin of the allantois and from this point back to its termination it forms a round rod, separated from contact with the endoderm by the second fusion of the two dorsal aortæ between it and the gut. It ends abruptly in the tail (plate 2, fig. 11) just beyond the termination of the dorsal aorta, at the same level as the end of the postanal gut, and here lies in contact with the medullary plate and widely separated by mesoderm from the postanal gut.

The notochord was found by Low (1908) not to extend as far caudad in embryo Pfannenstiel III as the gut; it did not pass into the tail, but ended over the cloaca. All other authors unite in stating that it passes into the tail, to fuse there with the tissues of the primitive streak—exactly what has been found in this case.

From the foregoing description it will be noticed that the stage of least development of the notochord is exhibited over the anterior part of the pharynx, the next stage over the hindgut, while the greatest is over the posterior portion of the yolk sac. The complete separation of the notochord from the endoderm is evident only in two regions, the first over the posterior two-thirds of the yolk sac, the second over the whole of the cloaca and postanal gut. In each case the two dorsal aortæ have fused between notochord and alimentary canal. Mesenchyme only passes under the notochord in one place, namely, just in front of the first fusion of the dorsal aortæ. The notochord lies in direct contact with the under surface of the nervous system throughout its whole course, with the exception of two very small intervals. The first is at the extreme anterior end, where a small amount of mesenchyme separates it from the floor of the brain. The second is where the cells of the first notochordal process are just beginning to burrow in around the notochord. All other notochordal processes of the sclerotomes come in contact only with the sides of the notochord.

In the cylindrical portions of the notochord the cells are large, fairly clear, and are arranged as a concentric layer with their nuclei near the periphery. The nuclei are large, round, and vesicular. A thin but definite cuticular membrane surrounds the notochord, except in those parts where it has still the form of an endodermal plate and is not yet cylindrical. Low also found no cuticular membrane in his embryo of 13–14 somites, in which the notochord was altogether in the form of a plate, except at the posterior end, where it was free.

In the embryos described by Van den Broek (1911) there is a cuticular membrane. These embryos are of 21 and 22 paired somites and the only place where the notochord is not free from the endoderm is over the pharynx. The absence of a membrane in this region is not mentioned. The embryo described by me is midway between these two and, as shown, the membrane is only present in the cylindrical portions.

I find confirmation, in this embryo, of the lumen found in the notochord by His (1880) in embryo L_1, 2.4 mm. long, and demonstrated by Eternod (1899) in three embryos of lengths 1.3 mm., 2.11 mm., and the third slightly larger but length unknown. In several places (plate 2, figs. 1, 4, and 9) there are distinct spaces in the very center of the cylindrical portions of the notochord. They are not very large, and do not extend over more than a few consecutive sections in any region, but they are perfectly distinct and appear like isolated parts of a lumen not yet completely occluded. In other regions the cells extend right in to the center, occluding the lumen, and frequently one or two extra cells are found in the center of the notochord. No recent investigators seem to have found evidence of this lumen except Grosser (1913), in the case of a very young embryo where the canal is very distinct. Some authors definitely state, indeed, that it is entirely absent, even in embryos not nearly as large as this one; such, for instance, being the case in the embryo of only 8 paired somites described by Dandy (1910).

At its posterior free rounded extremity (plate 2, fig. 11) the notochord is not of exactly the same structure as farther forward. Over the cloaca the radial arrangement of cells with a single peripheral layer of nuclei is lost. The cells become much more crowded and are irregular in disposition, with nuclei lying everywhere closely packed. This resembles very much the illustration of the posterior end of the notochord given by Low (1908). It ends by fusing with the tissues of the primitive streak, 2 sections later than the fusion of the postanal gut and 3 sections previous to the fusion of the medullary groove with the primitive streak. It here lies immediately under the medullary groove, but quite independent of it. This posterior portion has been described as ending in three different ways: First, by Low, it is said to end freely midway between medullary tube and cloaca, embedded in the mesoderm. Second, as exemplified by Ingalls and by Thompson, it runs in contact with the under surface of the medullary tube, but fuses posteriorly in the tail with the solid mass of mesoderm of the primitive streak. Third, as described by Bremer and Janošik, it fuses in the tail with the under surface of the nervous system, and this in turn with the primitive streak. The ending described by Low seems to be true of embryos up to the 13-somite stage, as two of 7–8 somites confirm this, one described by Dandy and one by Eternod (2.11 mm.), each having the notochord, as shown in the illustrations, not extending so far caudad as the gut. The second plan described is the normal one, as it is confirmed by the great majority of those who have described young embryos. Fusion with the nervous system into a common mass is really a fusion of each of these structures at a common level with the primitive streak.

Eternod (1899) is practically the only author who mentions the presence of a neurenteric canal in embryos of 2 mm. or more. In many descriptions of early embryos it is not mentioned, and it may therefore be inferred that it was not present, and Kollmann (1890) remarks positively, in an article on the notochord, that it had entirely disappeared in an embryo of 14 paired somites. Eternod found it well developed in an embryo of 1.3 mm., another of 2.11 mm., and says that in a third (larger again, but measurements omitted) appearances were practically the same as in the 2.11 mm. embryo. This last embryo had 2 gill clefts developed. Reckoning thus, Embryo VI, here described, is of the same stage of development. It is possessed of 18–19 segments, a distinct advance over the one mentioned by Kollmann, and yet it shows distinctly the neurenteric canal. This is, as far as I can ascertain, the oldest embryo in which this canal has yet been demonstrated. The location of this canal (plate 2, fig. 10) is in 4 sections immediately succeeding the caudal edge of the cloacal membrane, and it is represented by a solid rod-like connection between the upper

surface of the notochord and the under surface of the medullary groove in the median plane. There is now no lumen either in this neurenteric canal or in this portion of the notochord, it having been obliterated by the crowded, densely packed cells forming these structures. There is no doubt of this representing the neurenteric canal, as the structure is perfectly evident and distinct, and there is no solid tissue adjoining, with which it might be confused. The notochord extends caudad of the neurenteric canal for a distance of 8 sections (80μ) before fusing with the primitive streak. This is in accord with the findings of Eternod, for the notochord in his embryo of 2.11 mm. also passed caudad to the canal. In his case the only difference was the possession of a lumen by the structures, and thus of communication with the underlying gut. No communication with the gut occurs in Embryo VI, owing to the presence of the dorsal aorta between it and the notochord.

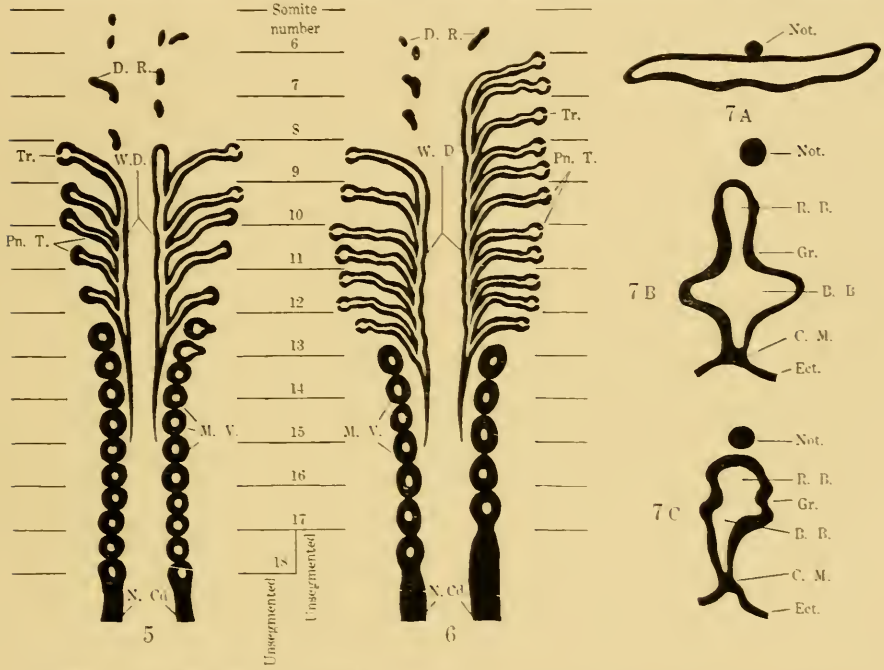
The close correspondence of Embryo V to its twin is nowhere better exemplified than in the development of the notochord. The description given above for Embryo VI will serve accurately for the account of the stages seen in Embryo V. It agrees in having the same extent, starting and ending at the same points as in its twin, in having fusions of the same degree with the endoderm and in exactly the same regions, both over the pharynx and over the hindgut. The main difference is that the dorsal aortæ are smaller and the areas of their fusions, one over the yolk sac, the other over the cloaca, are less in extent, so that not so long a stretch of the notochord is separated from contact with the endoderm. There is not as distinct an appearance of a lumen in this case, although there is a central space found twice, for two sections in each case, one just behind the pharyngeal region, one where the notochord becomes free from the gut over the cloaca. The neurenteric canal is equally as distinct here (plate 2, fig. 12) as in the other embryo and occurs at exactly the same level. In this case the dorsal aorta ends over the cloaca just before this level is reached and the notochord is very near the gut, and a solid cord of cells connects the notochord with the endoderm, exactly in line with the solid cord connecting the notochord with the medullary groove. The presence of such a distinct neurenteric canal in both of these embryos is a point of especial interest. The notochord ends by fusing with the primitive streak independently of either the nervous system or postanal gut.

ALIMENTARY SYSTEM.

The stomodæum here is merely the cleft (plate 1) between the head and the heart region. It is fairly wide and shallow and is closed off from the pharynx by the buccopharyngeal membrane. This membrane is perforated by three small apertures, marking the beginning of the rupture and disappearance of the structure. In Low's (1908) embryo of 13–14 somites, which is the nearest younger to this, the buccopharyngeal membrane is complete, while in the nearest older, Van den Broek's (1911) of 22 somites, only the remains of the membrane are to be found. In the two embryos last mentioned there is a distinct pouch of Rathke found, but no signs of this pouch are to be distinguished in Embryo VI, unless a small thickened portion of the ectoderm of the roof of the stomodæum, just in front of the buccopharyngeal membrane, be interpreted as such.

The pharynx (plate 3, figs. 1 and 2), just back of the pharyngeal membrane, is prismatic, appearing triangular on section, with the apex forming the notochordal groove dorsally. No pouch of Seessel is recognizable. As the branchial region is reached it widens out considerably and becomes flattened dorsoventrally. The gill pouches, 3 in number on each side, open widely off the cavity of the pharynx, there being practically no constric-

tion of the openings except a slight one for the first. The first pouch is very large and runs laterally and dorsally out to come into contact with the ectoderm, with which it is fused in two areas for a very short distance. The cephalocaudal diameter of the pouch is much greater than the dorsoventral, and its cavity is wide and capacious, but as yet undivided into dorsal and ventral portions. There is a very peculiar condition found here, however, for just before the lateral edge of the pouch is reached, a narrow villus-like ridge, filled with mesoderm, rises from the ventral wall of the pouch into the cavity, cutting off a narrow gutter in the extreme lateral part of the pouch. From the appearance of the sections this ridge is evidently not due to an infolding of the wall as the result of sectioning or mounting.



5. Diagram of nephrogenic system of Embryo VI.
6. Diagram of nephrogenic system of Embryo V. The numbers in text figures 5 and 6 indicate the level of the somites.
7A. Camera-lucida outline of the alimentary canal in Embryo VI, just cephalad of the yolk sac. Magnification × 120.
7B. Camera-lucida outline of the cloaca in Embryo VI, at the level of the cloacal membrane. Magnification × 120.
7C. Camera-lucida outline of the cloaca in Embryo V, at the level of the cloacal membrane. Magnification × 120.
For list of abbreviations see page 40.

The second pouch is not nearly so large as the first, but also reaches the ectoderm, with which it is fused over two small areas, with a narrow interval between. This pouch is wide for some distance as it leaves the pharynx, but only the most dorsal part reaches the ectoderm, appearing as a tapering, conical process of the larger portion. The third pouch is differentiated in front from the second by the presence of the intervening branchial arch, but can not be delimited behind, where it merges into the pharynx. This pouch does not extend far laterally, and so does not reach the ectoderm. It is somewhat pointed, as was the case with the second. Wallin (1913) describes only 2 pairs of gill pouches in an embryo

of 13 somites, but Low describes 4 in one of 14 somites, while here only 3 are present. Again, Van den Broek and Thompson, in embryos of 22 and 23 somites, find only 4, the fourth being small, so that evidently the fourth in Low's embryo is precocious in its appearance.

The median thyreoid anlage (plate 1 and plate 3, fig. 2) is present in this embryo and is very similar to that described by Low, being a rather wide shallow depression in the median line ventrally between the first and second gill pouches. In front of this is the large elevation of the floor of the pharynx caused by the underlying ventral aorta as it turns forward and divides into the paired aortæ. Wallin also found the median thyreoid anlage just caudad of the ventral aorta.

The relation of the notochord to the pharynx has been already fully described.

In the young embryos both older and younger than Embryo VI, the alimentary canal caudal to the pharynx becomes laterally compressed, forming a narrow dorsoventral passage giving rise to esophagus and stomach. This is not so in this embryo, where the gut slightly narrows laterally from the third gill pouch backward, still retaining a considerable lateral diameter, but showing the remarkable condition of being very markedly compressed dorsoventrally (text fig. 7 A), so that the lumen is almost slit-like. Over the sinus venosus this condition changes, as the gut begins to widen dorsoventrally again, and then it opens rapidly into communication with the yolk sac. On the ventral wall as it slopes toward the yolk sac, just behind the sinus venosus, a shallow depression runs forward, forming the liver bay, which is in about the same stage as seen in Low's embryo (1908).

No tracheal groove or lung anlage can be distinguished.

The opening of the yolk sac (plate 1) comprises one-third the total length of the embryo, and here the embryo is flattened out and there are no lateral constrictions and no way of locating the dividing line between yolk sac and body of the embryo. Back of this passes the hindgut, at first rounded in cross-section, but rapidly becoming ovoid or pear-shaped (plate 3, fig. 3), with the small end dorsally. As the cloaca (plate 3, fig. 3) is reached, a groove (text fig. 7 B) appears on each side between the large and small ends of the ovoid and almost cuts the cloaca into two separate chambers throughout its whole length. There is, however, a very narrow chink throughout the extent of the cloaca, where the two parts of the lumen (the rectal bay and the bladder bay) are in continuity. The rectal part of the cloaca is thus much compressed laterally and has a small oval lumen. The bladder portion is lozenge- or diamond-shaped, with dorsal, ventral, and two lateral angles, and the lumen of this part is very large. From this embryo it appears that the separation of the ventral part of the cloaca from the rectum is accomplished by the cutting in of two lateral grooves between them, and not by the extension caudally, as claimed by Felix (1912), of a gradually deepening saddle fissure starting just cephalad of the origin of the allantois. It also occurs much earlier than stated by Felix, who says the separation begins in embryos of 4.9 mm. nape length or 5.3 mm. greatest length. There is actual contact of the sides and every possibility of fusion along the lines of lateral constriction. The saddle-like constriction described by Felix, starting above the allantois, is not yet here indicated on the ventral wall of the gut, but the allantois quite clearly comes off the most cephalad portion of the ventral part of the cloaca. It runs ventrally (plate 1 and plate 3, fig. 3) in a gentle curve out into the belly stalk, with an umbilical artery on either side of it. The arteries unite in a blood reservoir above it in the stalk, where it at first lies ventral to all other structures. The common artery soon splits, however, and then reunites, forming a loop through which the allantois passes to a position dorsal to the artery and ventral to

the umbilical veins. A similar course has been noted for the allantois by Wallin (1913) in an embryo of 13 somites. This position it retains throughout the rest of its course to its termination, which is just before the chorion is reached. The allantois possesses a lumen throughout, although it is almost obliterated in some parts of its course in the belly stalk.

On the ventral surface of the body in the median line, just behind the belly stalk, is a shallow depression (plate 1 and plate 3, fig. 3) marking the position of the cloacal membrane, where the cloaca fuses with the ectoderm. The cloacal membrane is more than 2 cell layers in thickness, but the cells forming it lose their regular order, and are so irregular in shape and position that no definite number of layers can be recognized. The cloaca fuses with the ectoderm in two areas, both situated in the median line, with a free interval between, in which mesoderm is found. Just behind the level of the second area of fusion the grooves on the cloaca disappear and both bladder and intestinal bay open into a full rounded cavity contained in the postanal gut. This part of the gut is very short and ends in a broad, blunt surface, where the cells fuse with and are indistinguishable from the rest of the tissues in the tail region, here forming the primitive streak.

The alimentary system of Embryo V is different enough to merit a separate description and throws some very valuable light on appearances not very clear in its twin. The stomodæum and buccopharyngeal membrane of Embryo V are similar to those of Embryo VI, except that there is only one perforation of the membrane. As in the latter embryo, no pouch of Rathke is present and no distinguishable pouch of Seessel. The first branchial pouch is large and reaches to the ectoderm, with which it is only just coming into contact, and there is thus only a very small area of fusion. The entrance into this pouch from the pharynx is distinctly constricted. Near the distal end of the pouch 2 ridge-like villosities, lying on opposite walls, project into the lumen and cut off a very small terminal chamber in the pouch, communicating by the narrowed opening with the larger medial part of the pouch. These villosities are similar to that mentioned in describing the first pouch in Embryo VI. There is also a single one present in the second pouch of Embryo V. These villosities I interpret as being identical with the structure described by Grosser, in Keibel and Mall's Embryology, as being constantly present in the first gill pouch of all young embryos of about this age, and which he interprets as a rudimentary internal gill. He found this structure only in the first pouch, and evidently single, which is true here in the case of Embryo VI, but in Embryo V there are 2 ridges on opposite walls in the first pouch and 1 in the second pouch. If these represent internal gills, we would expect in favorable cases to find two lying opposite in a pouch, and would also expect indications of them in more than one pouch, so that the conditions found here ought to add considerable proof to this suggestion as to their significance.

The second branchial pouch is small and pointed and does not yet reach the ectoderm, as in Embryo VI, but is still considerably separated from it. The third pouch is small, pointed, and indistinct, and merged with the posterior part of the pharynx. In the median line ventrally between the first and second pouches is seen the anlage of the thyreoid gland. This is much more developed than in Embryo VI, and forms a large, broad pouch with a slightly narrowed neck, but has still a large lumen. The epithelium is somewhat thickened at the bottom of the pouch. This anlage lies directly caudad of the median ventral aorta and projects down deeply behind it.

Immediately in front of the thyreoid anlage the ventral aorta causes, as in Embryo VI, an immense median bulging of the pharyngeal floor. A deep groove lies to each side

of this, while a shallow one lies in the median line on the crest of the elevation. This third groove disappears, when followed caudally, on the down slope of the elevation, but the lateral grooves unite behind the elevation and then become suddenly the deep median groove or trough, forming the thyreoid, with its opening into the pharynx slightly constricted by the lips of the groove. These 2 lateral grooves have never been described in any other embryo, but their presence here is not an abnormal phenomenon. It is due to the immense size of the aortic stem that the floor of the pharynx is heaved up, forming a temporary stage of no special consequence, and this elevation and its consequent lateral grooves will quickly disappear, so that in stages such as shown by Van den Broek's and Thompson's embryos, the pharynx does not exhibit these peculiarities, and these grooves, being only incidental to the formation of the median elevation, are no longer found converging to form the beginning of the thyreoid gland.

The gut back of the gill pouches, as far as the yolk sac, is much compressed dorsoventrally, just as in Embryo VI, and consequently no esophageal and gastric region, which is in these early stages laterally compressed, can be recognized. In this portion of the gut the dorsal surface is smooth, the sides pointed, and the ventral surface wavy in outline on section. This latter condition is due to 3 or 4 longitudinal grooves on the wall. As the yolk sac is approached and the ventral wall begins to slope down behind the sinus venosus, a distinct median bay or outpouching forward is seen, which is the anlage of the liver (the liver bay). The communication between yolk sac and intestine is somewhat constricted to form a yolk stalk, so that this embryo does not lie wide open over the sac, as Embryo VI does. The hindgut is oval in cross-section, and passes insensibly into the cloaca, which is not quite so well developed as in Embryo VI, the main difference being that the cavity is not yet divided into two, although indications are present of an approaching differentiation. The stages here are valuable in showing the condition just previous to division. Here the lumen is large and capacious and on section appears triangular, showing a broad dorsal area and a ventral pointed portion (text fig. 7 c). On the lateral wall, in the broad portion, is a shallow furrow on each side, forming a small ridge projecting into the lumen. It is by the deepening of this furrow that the condition in Embryo VI is obtained, with the narrow dorsal rectal bay and the lozenge-shaped ventral bay almost completely separated. Fusion along the line of these opposing ridges would completely separate the rectum from the ventral part of the cloaca. The furrows outside, and consequent ridges inside the cloaca, are not well developed in Embryo V, but start about the level of the origin of the allantois and extend back beyond the level of the cloacal membrane, where they disappear. The postanal gut is very short and it very soon fuses with the tissues of the primitive streak. The cloacal membrane is marked by a depression on the outside of the body and the endoderm of the gut comes into contact and fuses with it for a short distance, and there are thickening and change in the epithelial layers of both ectoderm and endoderm.

The allantois, arising from the cloaca, runs cephalad, then ventrally into the belly stalk, where it lies for a long time ventral to the umbilical arteries, but finally, as in Embryo VI, passes through a loop formed by the arteries to lie dorsal to them. It is formed of a single layer of endoderm. The lumen is almost obliterated just after entering the stalk, and then becomes very large as the allantois lies under the umbilical artery, but becomes small again as it goes through the loop. The termination of the allantois is just at the chorion.

The remains of the neurenteric canal, as described under the notochord, fuse with the cloaca dorsally.

It will be seen from the foregoing that while the exact stage and degree of development of the various parts of the alimentary system in these twin embryos are not the same, yet in general they agree perfectly, showing the same plan of structure, and each helps to explain appearances found in the other. Taken together, they give valuable information as to the stage of the gut in the 18–19 somite stage of development, especially in regard to the gill pouches and the cloaca.

THE CIRCULATORY SYSTEM.

THE HEART.

The heart occupies the whole of the body ventral to the pharynx, and between the stomodæum in front and the septum transversum and yolk sac behind. This region is very prominent and bulging and the chambers of the heart are indicated on the outside by distinct protuberances. The pericardial cavity (plate 1) is very spacious and in the sections appears triangular, with walls nearly equal and angles all well-rounded, with a heart chamber lying in each angle, the atrium and atrioventricular canal dorsally and to the left, the ventricle ventrally, and the bulbus cordis to the right dorsally. The heart is still in the form of a simple tube, but is very strongly S-shaped, with abrupt flexures. At two of these flexures are the constrictions of the tube which mark the limits of the various chambers, visible both on the inside and outside of the muscular tube and also in the endothelial tube.

The muscular wall of the heart (plate 3, fig. 4; plate 4, figs. 1 and 2) is several layers thick, and forms a large, wide tube. The endothelium is 1 layer thick and forms a very small tube (plate 4, figs. 3 and 4) lying in the very center of the muscular tube and everywhere separated from the muscle by a considerable interval, which is entirely devoid of nuclei but shows many fine fibrillar processes and appears to contain a very clear, homogeneous matrix. In the sinus venosus and the atrium, however, the endothelium is closely applied to the muscular wall. Mall (1912), in an article on the development of the heart, states that that part of the tube forming the atrium can be very early identified by this disposition of the endothelium, the apposition of the latter to the muscle being complete in an embryo of 3.5 mm., while in the rest of the heart tube they are widely separated. The contact is complete here also, and there is an abrupt change at the atrial canal, where the endothelial tube becomes quite narrow and lies free from the muscle.

The heart as a whole resembles very closely that of embryo Pfannenstiel III, modeled by Low (1908), except that it possesses a much larger bulbus cordis, resembling in this respect the Meyer embryo modeled by Thompson (1907). Mall (1912) shows an illustration of the heart of an embryo of 3.5 mm. very similar in shape and appearance (both of the muscular and endothelial tubes) to the one here described.

The duct of Cuvier on each side passes into the septum transversum just lateral to the pleuroperitoneal passage (plate 1; plate 3, fig. 4; and plate 4, fig. 2) and is immediately joined by the immense trunk of the united umbilical and vitelline veins of each side, to form the horns of the sinus venosus. From here the main portion of the sinus venosus runs transversely, embedded in the septum transversum and joining the two horns. It is convex forward and its most forward portion issues from the septum, and has a very short piece of the dorsal mesocardium (plate 4, fig. 2) suspending it to the roof of the pericardial cavity. This ends at the beginning of the atrium. The atrium consists of a large chamber slightly subdivided on its surface by shallow dorsal and ventral longitudinal grooves, which unite at the anterior border. The atrial canal lies to the left, while the atrium runs forward a short distance in the median line, to end between the ventricle and bulbus cordis.

From the atrial canal the ventricle continues on at the left and runs far forward in the pericardial cavity, where it is strongly flexed ventrally and turns caudad as it reaches the median line. It is here attached to the pericardial wall by a short stretch of ventral mesocardium, the only portion of this structure which is still present. Wallin (1913) finds a similar attachment of the ventricle in an embryo of 13 somites. The lower portion of the ventricle runs caudad in the median line ventrally, until it lies under the atrium and end of the sinus venosus, when it turns very sharply dorsally to the left. There is a constriction at this flexure, and the cavity into which the ventricle here opens, which is almost as capacious as the ventricle itself, is the bulbus cordis. The bulbus now turns forward, running on the right side and parallel to the atrioventricular canal and the upper portion of the ventricle. Opposite where the ventricle begins to sink at the approach to its anterior flexure, the bulbus cordis begins to narrow in a funnel-shaped fashion, and at the same time this narrowed trunk turns medially and, reaching the middle line, goes suddenly up toward the roof of the pericardial cavity with a little twist backward, and then is immediately flexed cephalad outside the pericardial cavity and directly under the pharynx, in the floor of which it makes a very extensive elevation; this runs forward a very short distance only as the unpaired ventral aorta, and bifurcates just behind the second branchial pouch. The peculiar loop formed at the end by the bulbus cordis in the embryos of 22 and 23 somites, described by Van den Broek (1911), is not seen here, but it would not take a great deal of displacement or increased flexure of the funnel-shaped portion to produce something like it. The bulbus cordis forms the part of the heart which reaches farthest cephalad and so the heart prominence is much greater and farther forward on the right than the left, as is the case in the Van den Broek embryos and in the one described by Thompson. It will be seen that the heart of this embryo is intermediate between those of stages already mentioned as either just earlier or just older.

There is a small piece of dorsal mesocardium (plate 3, fig. 4, and plate 4, fig. 2) extending to the roof of the pericardial cavity from the dorsal surface of the bulbus cordis. This membrane is much vacuolated and evidently in process of degeneration. A similar remnant of dorsal mesocardium in this location has also been described by Wallin (1913).

The heart of Embryo V is so similar to that of Embryo VI as to merit no mention except in two particulars. The chambers, flexures, and constrictions of the tube are an exact replica of those already described, but the bulbus cordis projects considerably more cephalad of the rest of the heart than in Embryo VI, and the anterior part of the pericardial cavity for some distance contains only the bulbus cordis and aortic stem. The only other difference is the presence, on the atrium, of a much deeper and more distinct groove dorsally, so disposed that it does not lie in the median plane, but, starting just in front of the left horn of the sinus venosus, runs obliquely toward the middle line, dividing this part of the heart very distinctly, so that to the right of the groove lie the combined sinus venosus and atrium, and to the left only a portion of the atrium.

The correspondence of the hearts of these two embryos to the heart of embryo Hal 2, modeled by Weintraub, and figured in Keibel and Mall's Human Embryology, is even closer than to the hearts of the Low and Thompson embryos. Of course there is a certain individual difference in general appearance, but the disposition, relations, and sizes of the various chambers and the amount of flexure show a most remarkable similarity. This embryo is 3 mm. long and possesses 15 paired somites, and so is the nearest in general development of all those quoted to the two here described. In all three embryos the ventricle is by far the largest portion of the heart, and the bulbus cordis is next in size.

The ventricle resembles a letter U laid on its side, so as to have dorsal and ventral limbs and a flexure looking cephalad, and with the atrium lying over the open end.

THE ARTERIES.

From the unpaired ventral aorta, where it bulges up under the floor of the pharynx, arise the right and left ventral aortæ (plate 4, fig. 1), just back of the second branchial pouch. They diverge like the limbs of a letter V, and as they run forward form a prominent ridge in the floor of each side of the pharynx. There is no definite end to them, since each passes imperceptibly into the first branchial arch vessel, which is (plate 1 and plate 3, fig. 2) almost as large as the ventral aorta from which it springs, and runs cephalad and dorsally in front of the first gill pouch, and then arching caudally over the pouch turns into the dorsal aorta. From the outer side of each ventral aorta arises the second branchial arch vessel (plate 1 and plate 3, fig. 2), which is only half the caliber of the first, but is complete, possesses a lumen, and communicates with the dorsal aorta by running dorsally between the first and second gill pouches, in an arch convex laterally, while the first arch was convex forward. There is a slight bud posterior to this, which is the first indication of the third branchial artery. This embryo fits in perfectly in the series of early embryos, in development of the aortic arches. Dandy's embryo (1910) of 7 somites possesses one completely formed, the first arch, with small buds of others posterior to this. Low (1908) in the embryo of 14 somites finds the first arch complete, the second being formed. Then comes the embryo of 18–19 somites here described with two arches, the second just complete, and immediately following is the embryo of 23 somites described by Thompson (1907), which shows two complete arches.

The two dorsal aortæ begin anteriorly, directly continuous with the first branchial arch vessel, and are situated far out at the sides of the pharynx. As they run caudally they very gradually approach each other, and finally, about half way back over the yolk sac (plate 1) they fuse beneath the notochord, presenting an hour-glass shape as seen in the cross-sections, showing that fusion has only just occurred. This area of fusion extends from the eighth to the thirteenth somite, inclusive, and then the two aortæ again separate, but lie in close contact with the gut and notochord. At the level of the succeeding 4 somites are the roots of origin of the right and left umbilical arteries (plate 1) from the aortæ. These arise from a series of large ventral branches of the aortæ, which lie alongside of the gut, from the end of the yolk stalk to the beginning of the allantois. These all anastomose and give rise to the umbilical artery. This origin is in accord with the latest investigations of Felix (1912) and others. It will be seen that at this stage the umbilical artery arises opposite the third to sixth thoracic segments. In two embryos studied by Felix, one younger, one older, the origin of the umbilical artery is respectively cranial and caudal to this. In the younger embryo, Pfannenstiel III, of 14 somites, the origin of the umbilical artery is opposite somites 12, 13, and 14, then in this embryo of 18–19 somites it is opposite the fourteenth to the seventeenth, and in the Meyer embryo of 23 somites is opposite the unsegmented mesoderm posterior to the somites. At the commencement of the unsegmented mesoderm in Embryo VI, over the beginning of the cloaca, the two dorsal aortæ fuse a second time, and form a vessel in the shape of an inverted letter U from here to their termination, which is coincident with the end of the gut. This description applies to the muscular tubes of the arteries. The endothelial tubes are very small, often indistinct, and as far as can be ascertained do not fuse similarly to the muscular ones, so that the endothelial aortæ are separate throughout their entire extent.

This embryo is unique in two particulars. First, it is the youngest embryo recorded in which there is any fusion of the dorsal aortæ. Those nearest to it and younger, such as that described by Low, have still no fusion whatever, while in those just older, such as described by Thompson and Van den Broek, the dorsal aortæ are fused over the yolk sac. In Thompson's case the somites at the level of fusion are given, and include only one more than in Embryo VI, in his case being from the seventh to the thirteenth, in this case the eighth to the thirteenth. The second unique feature is the second fusion of the aortæ in the caudal region, where even in older embryos paired aortæ are found. It will be noticed also that in the region between fusions the aortæ lie very close together, only the narrow notochord lying between them. The aortæ show their largest caliber around the origin of the umbilical arteries and just posterior to this.

The branches of the aortæ are numerous. There is no sign of forward extension of any artery into the head as the internal carotid on the right side, but there is a short branch on the left (plate 1; plate 3, fig. 1) continuing forward in the line of the dorsal aorta to a point just in front of the hypophysis cerebri. There is a dorsal intersegmental artery (plate 1) between every two somites back to the depth of the concave dorsal bend. Posterior to this point the sections cut the body in a plane unfavorable for finding these arteries, and it can not be stated whether they are present or not. There are many primitive vitelline arteries (plate 1) given off as ventrolateral branches both of the paired and unpaired aortæ, and these ramify over the wall of the yolk sac. The roots of the umbilical arteries are in series with these. Dorsolateral branches of the aorta run to the pronephros and cranial half of the mesonephros. Arteries to the gut and urinogenital system were not counted, as they were hard to detect and in some cases, where the shape of the aorta indicated the origin of a branch, the branch could not be followed. Counting would thus not give any accurate number and so was abandoned.

The umbilical arteries run out into the belly stalk, one on each side of the allantois, and unite dorsal to the allantois, as they all turn into the stalk. This common vessel is of immense size and filled with blood, forming a blood reservoir (plate 1), as in the embryo described by Dandy (1910). A short distance out in the belly stalk the artery divides, and then immediately unites again, forming a loop through which the allantois passes as it proceeds from a position ventral to the artery to one dorsal to it and ventral to the veins. The artery is now single all the way out to the chorion, where it divides into two, each of which ramifies over one-half of the chorion, supplying the villi.

The arteries in Embryo V are somewhat smaller and are much harder to follow than in Embryo VI, part of the difficulty being due to their being so filled with blood in many cases as to be almost indistinguishable from the surrounding mesoderm. There are two branchial arch vessels on each side, the second of which is only just complete. The dorsal aortæ are fused from the ninth to the thirteenth segments, one less than in Embryo VI. The origin of the umbilical artery on each side is from the fourteenth to seventeenth segments and the caudal aortæ are fused over the cloaca as in the other embryo. The aorta terminates here shortly before the end of the gut, allowing the persistence of that part of the neurenteric canal between the notochord and the gut, as already described.

VEINS.

The only veins as yet developed are the primitive embryonic trunks.

The vena capitis medialis (plate 1) is present on each side, beginning in the region of the optic vesicles. It can be traced caudad, without any interruption, to just in front of

the first somite, where it turns out laterally into the anterior cardinal. The vena capitis medialis lies throughout its course close in against the side of the brain and passes ventromedially to the trigeminal, acusticofacial, glossopharyngeal, and vagus ganglia and the otocyst. It lies so close against the trigeminal ganglion, whose under surface is irregular, as to give the appearance of penetrating it. In embryos described by Ingalls (1907), Broman (1896), and Mrs. Gage (1905), which are somewhat older than this embryo, the vein lies lateral to the acusticofacial ganglion. Mall (1905) states that the first position of the vein is medial to the ganglia, but that loops form around them and the medial branch disappears, leaving the vein lateral to all but the trigeminal. This process has not yet begun in this embryo of 18–19 somites, but is completed in Mrs. Gage's of 27 somites.

The anterior cardinal vein (plate 1 and plate 3, fig. 4) is the direct continuation of the vena capitis medialis, where the latter turns out in front of the first somite. The anterior cardinal vein lies lateral to the somites and on the right side extends to the middle of the third, on the left to the beginning of the third somite, where it ends in the duct of Cuvier. The finding of the duct of Cuvier at this level is evidently normal for early stages, as Evans, in the account of the vascular system in Keibel and Mall's Human Embryology, places it here, and Williams (1910), in chick embryos of 15 and 18 somites, also found it at this level.

The posterior cardinal vein (plate 1 and plate 3, fig. 4) is as yet very short, and can only be traced back from the duct of Cuvier to the sixth somite. Beyond this it is not recognizable, though isolated spaces, apparently vascular, occur along the line of its future course. This is the youngest embryo in which the posterior cardinal vein has yet been found. It is only a very short trunk in the embryo of 23 somites described by Thompson, and in Bremer's embryo of 4 mm. it is only a very small bud situated on the duct of Cuvier.

The vitelline veins (plate 1) commence in a plexus over the yolk sac and run forward in the wall of the yolk sac near the body wall and parallel to the long axis of the body. At the anterior surface of the yolk stalk they turn upward into the body, being situated in the septum transversum and immediately lateral to the pleuroperitoneal passage. Just in front of the opening of this passage into the cœlom each unites (plate 3, fig. 4) with the umbilical vein of the corresponding side. There are no veins or anastomosing channels uniting the vitelline veins of the two sides anteriorly; their only communication here is through the sinus venosus, but such communications occur, Low (1908) describing one in an embryo of 14 somites.

The umbilical veins, two in number, start in the chorion and enter the belly stalk, running in its dorsal portion (plate 1), and as the belly stalk broadens out, they lie in its dorsal angles just under the reflection of the amnion from it. In the belly stalk the veins show frequent anastomoses, forming a blood sinus similar to that described by Dandy (1910), and finally separate to enter the body, one on each side. They run forward in the somatopleure, forming a bulging ridge under the line of reflection of the amnion. On reaching the septum transversum each unites with its respective vitelline vein into a large common trunk (plate 3, fig. 4) which receives the diminutive duct of Cuvier, as they all pass into the sinus venosus.

The description of the veins of Embryo V is essentially similar to the above. The posterior cardinal vein can not be so distinctly followed, however, and there is an interval in front of the first somite where the vena capitis medialis can not be distinguished. These veins, however, may be present, for vessels in this embryo are hard to follow, and serial sections, it is well known, do not give the best results unless the vessels have been previously injected.

THE URINOGENITAL SYSTEM.

The urinogenital system is in a very early stage of its development. There is a definite area of the cœlomic wall, the middle plate of the body, between splanchnopleure and somatopleure, which extends back as far as the sixteenth somite on each side, forming the Wolffian or urinogenital fold. Beyond the sixteenth somite this portion of the wall is not formed, the splanchnopleure and somatopleure meeting at a narrow angle. All the nephrogenic tissue is found in the urinogenital fold or located at the angle behind it. This fold begins gradually anteriorly, increasing in size as it proceeds caudad and then decreasing again rapidly in the last few segments.

The description following is for the right side (text figs. 3 and 5) in Embryo VI, which shows the greatest development in this embryo. The structures exhibit a close correspondence to those described by Felix in Keibel and Mall's Human Embryology.

In the first three somitic segments no trace whatever of nephric tissue can be identified, although tubules have been described in these segments, Dandy (1910) finding them in the first two in an embryo of 7 segments. If they were ever present in Embryo VI they have completely degenerated. In segments 4 and 5 there are small, compact masses of cells embedded in loose tissue in the nephric region, their appearance very much suggesting parts of tubules, and in the sixth, seventh, and eighth segments remains of tubules even more distinct are to be found, and in these segments is also to be found a portion of the intermediate cell mass from which these tubules arose. In the sixth segment this is attached only to the cœlomic epithelium, and in all the remaining segments it is connected with both the somite and the cœlomic epithelium. Mrs. Gage (1905), describing an embryo of 4.3 mm. with 28–29 somites, says: "The connection which probably existed between the myotome and the cœlom through the intermediate cell mass which gives rise to the blastema forming the tubules is of an earlier stage than these here considered." She says she has observed this in the chick, and it has been found in the rabbit. I can confirm her supposition of its presence in the human embryo of early stages, as it is quite evident in a few of the segments in this present embryo and also in its twin.

At the cephalic boundary of the ninth segment the Wolffian duct begins and also a well-developed pronephric tubule, which arises from the dorsal or lateral wall of the intermediate cell mass, passes dorsally, and then turns caudad and opens into the Wolffian duct. Starting from the intermediate cell mass of the tenth segment are two large pronephric tubules, one beginning at the cephalic edge of the segment, the other in the caudal half. Projecting into the cœlom in this region, just ventral to the attachment of the intermediate cell mass to the cœlomic epithelium, is a fairly solid, club-shaped protuberance with a slightly narrowed stalk, in which can be seen a blood-vessel. I think that this may unhesitatingly be called an external glomerulus. It is the only one occurring in this embryo. Janošik (1887) also found a single external glomerulus in a 3 mm. embryo. In the eleventh segment there is a pronephric tubule, not so large as those in the tenth, and in the twelfth is a still smaller one. These tubules all run caudally under the Wolffian duct, which lies dorsal and lateral to them, and they open into the duct in the segment behind the one in which they arise. The Wolffian duct and the tubules, and the intermediate cell masses of these segments, all contain lumina.

Behind the twelfth segment there is a sudden change in the nephric system. The Wolffian duct (text fig. 5) receives no tubules and rapidly decreases in size, loses its lumen, and becomes flattened and crescentic in outline, lying applied to the dorsolateral surface of the nephrogenic cord. It approaches the ectoderm and ends just beneath and in con-

tact with the latter at the beginning of the sixteenth segment. Whether there is actual fusion can not be stated, but it may be emphasized that immediately in this vicinity, around the end of the Wolffian duct, the ectoderm shows absolutely no change and no preparation for further formation of the Wolffian duct and its growth caudad. The evidence here corresponds exactly with that obtained by Felix (1912) and supports his view of the formation of the Wolffian duct by fusion of the ends of pronephric tubules anteriorly, and the caudal extension of it to the cloaca by growth of the tip, or splitting off of cells from the nephrogenic cord; it also strengthens materially his statement that he would deny any participation of ectoderm in the formation of the duct. This embryo comes midway between two described by him, one of 13–14 segments, having no duct yet formed, and one of 23 somites, where the duct nearly reaches the cloaca.

From the thirteenth to eighteenth segment, inclusive, the character of the nephrogenic tissues is similar, forming a large rounded mass of cells in each segment, connected on one side by a narrow string of cells to the somite, on the other side to the cœlomic epithelium. On them are small protuberances in the thirteenth and fourteenth segments, suggesting the origin of tubules from them. These masses (text figs. 3 and 5) are all continuous, forming an unbroken nephrogenic cord, but there are at intervals small central lumina, so that the cord is practically a fused series of vesicles. It is rather difficult to determine the exact number of mesonephric vesicles present, as the lumina are not all distinct, but there are either 10 or 11. There is thus no numerical agreement with the number of segments in which they lie, a fact universally true in all human embryos described. Fusion with the cœlomic epithelium is very extensive, beginning at the seventeenth somite, and the line of division between the epithelium and nephrogenic cord is marked by a furrow which gradually disappears by the time the unsegmented mesoderm is reached. Marked fusion also occurs with the nineteenth somite, which is not entirely formed, and the line of division between somite and nephrogenic cord is very soon lost, and the intermediate cell mass, which here represents the nephrogenic cord, very soon also loses its identity—the somitic plate, intermediate cell mass, and lateral plate all blending in one common, undifferentiated mass of mesoderm.

The fully developed tubules of the ninth to twelfth segments are called pronephric, principally because the Wolffian duct is just in process of formation and is being formed by their union—according to Felix (1912) mesonephric tubules never appear until after the formation of the Wolffian duct—and also because other authors have found pronephric tubules at this same level in young embryos possessing 23 paired somites or less. The abrupt change from pronephric tubules developed as far as the twelfth segment to mesonephric vesicles beginning in the thirteenth is in thorough accord with the emphatic statement of Felix that in the human embryo pronephric tubules are never developed caudal to the twelfth segment, which is the first thoracic.

As to the presence of openings of the nephric tubules to the cœlom (the nephrostomes or trichter) there is some doubt, but it may be mentioned that in several segments there is a cleft in the cœlomic epithelium at the point where the intermediate cell mass fuses with it, and in some cases this even opens into the cavity of the intermediate cell mass. But this may be an artifact, and indeed it is simulated by occasional breaks in the cœlomic epithelium in other places, so giving rise to doubt as to its actual significance. There are, however, two undoubted openings to the cœlom, each situated in a depression of the cœlomic wall. These openings (text fig. 5) are the nephrostomes of the first two pronephric tubules, one in the ninth segment, the other in the tenth. The connection of the inter-

mediate cell mass in segments caudad to this occurs at the point of a slight depression in the wall of the cœlom, but there is no definite, funnel-shaped opening present.

The left side of this embryo (text figs. 3 and 5) is very similar to the right, but slightly less developed. In the first 5 somitic segments tubal remains are very few and are small and hard to distinguish from the surrounding mesenchyme. The intermediate cell mass is recognizable from the sixth segment back to the unsegmented mesoderm. The first recognizable tubule is in the caudal portion of the ninth segment, starting from the cœlomic epithelium, and at this point there is a funnel-shaped depression forming the nephrostome. The tubule soon separates from the epithelium and runs dorsally and then caudally, forming the beginning of the Wolffian duct, there being no little blind end of the duct in front of it, as on the right side. There are 5 pronephric tubules in all, the first being the only one possessed of a nephrostome. The others are found, 2 in the tenth segment, 1 each in the eleventh and twelfth; each has a lumen and unites with the Wolffian duct. The duct is very large here, but rapidly decreases in size, becoming crescentic and solid, as it runs caudally, and ending as a rapidly narrowing string of cells. There are three cells in the section before the end, and one cell finally at the end, in contact with the ectoderm, at exactly the same level as on the right side, namely, between the fifteenth and sixteenth somites.

Embryo V shows even much better than Embryo VI the development of the pronephros, which is nearly double the size of that found in Embryo VI, while the mesonephric anlage contains only about half the number of vesicles found in the latter. This surprising difference is the more remarkable because in all other organs the two embryos present an almost completely equal and parallel development. In the matter of somites formed it will be remembered Embryo VI has 18–19 and Embryo V has 17–18, and it would not be expected that a difference in development of only one somite would mean so great a difference in the urinogenital system as is here manifest.

The urinogenital folds extend from the third somitic segment, on the dorsal wall of the pleuroperitoneal passage, to the caudal end of the sixteenth segment. The intermediate cell mass is present from the fourth segment on the left and the fifth on the right, back to the unsegmented mesoderm, and is connected to the somite and to the cœlomic epithelium in each segment. Remains of tubules in front of the pronephros can not be seen on the right side. The pronephros (text figs. 4 and 6) begins on this side with two fully formed tubules in the seventh segment. Following this tubules occur as follows: 1 in the eighth, 2 in the ninth, 1 in the tenth, 2 in the eleventh, 2 in the twelfth, and 1 at the beginning of the thirteenth segment, making a total of 11 tubules. In each case there is a distinct trichter or nephrostome by which the tubule communicates with the cœlom. Each tubule is budded dorsally from the intermediate cell mass, forming the principal tubule as described by Felix (1912), the intermediate cell mass forming the supplementary tubule, and by the fusion of the ends of the principal tubules the Wolffian duct is formed, which therefore extends from the seventh segment. It receives no connections beyond the last pronephric tubule, but extending caudally, overlying the nephrogenic cord, ends at exactly the same point as the duct of each side in Embryo VI, namely, between the fifteenth and sixteenth segments.

Posterior to the pronephros the intermediate cell masses have fused to form a solid string, the nephrogenic cord, which contains small cavities at intervals, forming mesonephric vesicles, of which there are 5, the last being in the seventeenth segment.

On the left side, as in Embryo VI, development is not quite the same as the right, being a little less (text figs. 4 and 6). There are 7 pronephric tubules, the first appearing

in the ninth segment, 2 caudad of the first on the right. Following it are 1 in the tenth, 2 each in the eleventh and twelfth, 1 in the beginning of the thirteenth. There is a nephrostome present for all except the last tubule. The Wolffian duct is similar to that of the right side and extends caudally to exactly the same level. In front of the first tubule, for two segments, doubtful remains of tubules are seen. The nephrogenic cord beginning in the thirteenth segment contains 7 mesonephric vesicles, 2 more than on the right, the first being in the thirteenth segment, the last in the eighteenth.

The embryos standing nearest to these two in development of the urinogenital system show many interesting points of comparison. Embryo Pfannenstiel III, modeled by Low, the urinogenital system of which is specially described by Felix (1912), possesses 13–14 somites and the pronephros is just beginning its development. There are rudiments of it in the second, fourth, and sixth segments, a separate tubule in the seventh, 2 united in the eighth and ninth, and two pronephric ridges on each side of the body, united end to end and connected to the tubules as far as the fourteenth somite. There is no Wolffian duct. The presence of this pronephric anlage back as far as the fourteenth somite is interesting and leads to the question whether pronephric tubules may not be found caudad of the twelfth segment, which Felix has stated to be the extreme limit of their occurrence. This would give a reasonable explanation of the conditions found by me, for although Embryo VI has no tubules beyond the twelfth segment, Embryo V has one on each side in the thirteenth. There is a gap in the series described by Felix, in the very middle of which come the two embryos here described, and then comes Felix's second example, the Meyer embryo of 23 paired somites, modeled by Peter Thompson, Felix studying specially the urinogenital system. Here there are 7 pronephric tubules, lying opposite the ninth to twelfth somites, the first separate, the others united, forming the Wolffian duct, which extends caudad to the twenty-second somite. From the thirteenth to the beginning of the sixteenth somite lie 8 mesonephric vesicles in a chain, continuous from the latter point to the unsegmented mesoderm with the nephrogenic cord.

The above-mentioned embryo, although advanced 4–5 somites over the two described in this paper, shows a nephric system intermediate between the two, more tubules and fewer vesicles than Embryo VI, fewer tubules and more vesicles than Embryo V. The most noticeable difference is the caudal extension of the Wolffian duct over 6 additional segments, it reaching only to the sixteenth segment in both the twins. It will be noticed that from a condition with no Wolffian duct at the 14-somite stage we pass to one in the 18–19 somite stage with a duct extending over from 7 to 9 segments and in the 23-somite stage extending over 14 segments. There is thus a very rapid caudal growth of the free end of the Wolffian duct, it soon reaching the unsegmented mesoderm, and from now on, as records show, it keeps pace with the formation of the somites and reaches the cloaca at the 27-somite stage, although it does not penetrate until later.

The urinogenital system has been described by MacCallum (1902) for an embryo of 19 somites, length 3.5 mm., which is thus almost exactly comparable in its general development to the two here described. In this embryo MacCallum found a single duct lying in the sixth to ninth segments, connected to the cœlom at a depression opposite the sixth somite. There was then a break, and opposite the tenth segment the Wolffian body began and extended to the unsegmented mesoderm, having 13 thickenings on it, regarded as developing mesonephric tubules. MacCallum interprets the small anterior mass as a rudimentary pronephros. Evidently there is here one pronephric tubule and a short stretch of Wolffian duct. This Wolffian duct has not half the length shown in the two

embryos described by me, although all three embryos are at the same stage reckoned by the number of somites. In an embryo of V. B. length 4.5 mm., N. B. length 5 mm., he finds a short stretch of duct with one tubule on it, opposite the seventh somite, then beginning at the eighth somite, the Wolffian duct with 15 mesonephric tubules on the right, 17 on the left. Mrs. Gage (1905) found one isolated tubule in the eleventh segment, separate from and just cranial to the beginning of the mesonephros, in embryo 148, three weeks old and possessing 27–28 somites. In two others of similar age she found similar isolated tubules. Tandler (1907), in an embryo with 38 paired somites, found isolated tubules and one glomerulus (presumably external) in front of the mesonephros, but does not state in what segments. Janošik (1887) in a 3 mm. embryo found two isolated pronephric tubules with nephrostomes, and an external glomerulus in front of the mesonephros. Bremer (1906), in a 4 mm. embryo, found cranial to the mesonephros 3 isolated tubules, the first opening into the cœlom, at the level of the liver, by a nephrostome. The mesonephros in all these cases is well developed. Pronephric tubules have thus been found persisting for a long time and always in the region of the seventh to twelfth somites, shown to be that of the greatest development of the pronephros in the two embryos here described and also in those of Felix. If this region degenerated with anything like the rapidity of the parts of the pronephros cranial to the seventh somite (and pronephros is present here also, as shown by the tubules in Dandy's embryo and remains in older ones), these tubules enumerated above would disappear long before they do, so that their persistence in this region is rather an interesting fact.

Regarding the external glomerulus, Felix states that it does not appear until the pronephros is in full process of degeneration. This agrees with its occurrence in Tandler's and Janošik's embryos, and if the statement is true the presence of a glomerulus in Embryo VI and none in Embryo V will explain why the former exhibits only half the number of pronephric tubules found in the latter; Embryo VI therefore shows an advance in the nephric system over that in Embryo V more than commensurate with the possession of only one extra pair of somites, and this advance is further shown by the possession of nearly double the number of mesonephric vesicles that occur in Embryo V.

Felix (1912) remarks as to the Meyer embryo: "Whether this concentration of six pronephric tubules within the limits of $3\frac{1}{2}$ body segments indicates a primary dysmetamerism or has resulted from the approximation of originally more separated anlagen can not be determined." This suggestion of primary dysmetamerism in the formation of the pronephric tubules is very interesting, as it will be remembered in both Embryos V and VI several of the segments gave rise to 2 tubules each. There are 10 tubules in all in Embryo VI, 18 in Embryo V, of which respectively 4 and 12 are found in pairs (2 opposite 1 somite), making a total of 16 out of 28 tubules showing evidence of dysmetamerism. In the mesonephric anlage no definite arrangement of vesicles according to segments is to be found.

Regarding the genital cells and ridges there is little to say. Between the cloaca and the mesoderm of the body, in a few instances, were masses which might have been either multinucleate cells or very solid clumps formed by a few mesenchyme cells. They resemble the cells known as wandering or primary genital cells, 2 of which, from embryo Pfannenstiel III, are shown in a figure in Keibel and Mall's Embryology. Whether the cells I have seen are actually genital I am not prepared to state, owing to a certain amount of maceration of mesoderm in this region. No genital ridge is yet present. The cœlomic epithelium is 2-layered on the medial side of the urinogenital fold and around the angle from this on to the root of the mesentery. It is thinner in the region of the nephric tissues and 2-layered

again at the reflection on to the lateral body wall, so that evidently its thickening at the root of the mesentery is not significant, although it is heavier than the other thickened portions and occasionally is irregularly heaped up in more than 2 layers at points just medial to the pronephros.

THE SEPTUM TRANSVERSUM AND THE CŒLOM.

The septum transversum is very much like the one described by Peter Thompson (1908) for the 23-somite stage, but is situated (plate 1) further cephalad, being opposite the first 2 somites in this case. It is also not inclined obliquely from the dorsal surface caudally and ventrally, but is nearly horizontal. It is convex ventrally and immediately behind it is the yolk sac. In the dorsal portion the liver bay lies embedded. The septum is completely attached to the body wall laterally and ventrally, but not dorsally, for to each side of the gut lies the pleuroperitoneal passage of the cœlom, passing dorsal to the septum. To the dorsal body wall the septum is attached by two lateral horns, one lateral to each pleuroperitoneal passage, and in the median line it fuses with the mesoblast surrounding the gut. Its cephalic surface dorsal to the sinus venosus has attached to it the dorsal mesocardium, which latter is prolonged forward from it in the median line, over the small free portion of the sinus venosus.

Contained in the tissues of the septum transversum are posteriorly the vitelline and umbilical veins of each side, which enter it from the lateral body walls, while passing laterally over the pleuroperitoneal passage and running ventrally into the septum, lateral to the passage, is the duct of Cuvier of each side. The vitelline and umbilical veins of each side unite into an immense common trunk in the septum, and with this trunk unites the duct of Cuvier, the total union forming in the septum the horns of the sinus venosus. These horns are united by the median, transverse, crescentic part of the sinus, which is embedded in the anterior part of the septum, except a small portion which escapes from the septum just before opening into the atrium.

The pericardial portion of the cœlom has been described in connection with the heart. It is large and capacious and forms one large chamber, except dorsally over the atrium and again over part of the bulbus cordis and over the aortic stem, where the dorsal mesocardium subdivides it into two. The most cephalic part of the cavity is that surrounding the bulbus cordis, where the cavity reaches a level just in front of the beginning of the otocyst. This corresponds exactly with the findings of Mrs. Gage (1905). The pericardial cavity rapidly narrows posteriorly to each side of the dorsal mesocardium, and from this portion the pleuroperitoneal passage proceeds caudad, dorsal to the septum transversum. This passage lies on a level with the gut and is at first hook-shaped, curving round the dorsal and medial surface of the horn of the sinus venosus. As it passes back it comes to lie altogether on the median side of the vitello-umbilical venous trunk, and is very much compressed laterally, the long axis of the lumen being dorsoventral. At the level where the vitello-umbilical trunk is split into its components, the vitelline and umbilical veins, which level is also the point of transition of these veins to the septum transversum from the body wall, the pleuroperitoneal passage becomes rounded and immediately opens into both the endocœlom and exocœlom. The endocœlom and exocœlom are in wide communication for over one-third the total length of the embryo, from the level of the posterior edge of the septum transversum to the beginning of the belly stalk.

At the level of origin of the belly stalk the splanchnopleure and somatopleure unite to cut off communication between the endocœlom and exocœlom. The endocœlom lies to each

side of the gut and is roughly oval in section, with its long axis dorsoventral. It rapidly decreases in size and ends at the sides of the cloaca at the level of the cloacal membrane.

There is thus, just as Dandy (1910) and Wallin (1913) have described in younger embryos, a continuous circuitous route through the body of the embryo from the exocœlom of one side to that of the other, by way of the endocœlom, pleuroperitoneal passages, and pericardial cavity. The question as to whether the cavities of the somites communicate with the endocœlom is doubtful in many cases, owing to a slight maceration of the lateral parts of the somites in the most favorable region for answering this. There is, however, in a few cases in Embryo V, direct continuity of the cavity of the somite with the lumen of the intermediate cell mass, which in turn opens through the nephrostome into the endocœlom.

The septum transversum and cœlom of Embryo V are exactly similar in all respects to the above.

SENSE ORGANS.

THE INTERNAL EAR.

The only sense organ yet in evidence is the internal ear, excepting of course the optic vesicles. No lens thickening and no olfactory placode are yet to be found.

The internal ear is in the stage of the auditory cup, still widely open to the exterior. It lies directly dorsal to the region of the second gill cleft. It is an egg-shaped invagination of ectoderm, 3 to 4 layers of cells thick and surrounded, except on its medial side, by mesoderm of the head. Medially it lies to the side of the hindbrain, and between it and the brain is the hinder part of the acusticofacial ganglion, while the rest of the ganglion extends out directly in front of it. The shape of the cavity throughout is rounded, with no indications of the approaching division into pars superior and inferior, already beginning to show in Van den Broek's (1911) embryo, only 4 somites in advance of this in development. In Low's (1908) embryo, 4 somites less than Embryo VI, there is only the slightest depression, the thickened ectoderm mainly indicating this sense organ, and Wallin (1913) describes an embryo of 13 somites with no evidence whatever of the invaginations. In Van den Broek's embryo the opening from the outside is not equal in extent to the cup, but is much constricted, being only 40μ long, while the cephalocaudal diameter of the cup is 184μ. In Embryo VI the opening comprises almost the whole cephalocaudal extent of the cup and so even the extremities of the cup are not as yet constricted off from the ectoderm. The auditory cups of Embryo VI are slightly larger, but those of Embryo V are entirely similar in every way to the others. The main measurements are appended for both. These measurements were not taken in the plane of the principal axes of the body of the embryo, but in the plane of the principal axes of the auditory cup alone, which, lying on the sloping body wall, has its axes oblique to those of the body.

Outside diameters of auditory cup.	Embryo VI.		Embryo V.		Van den Broek's embryo.
	Right.	Left.	Right.	Left.	
Cephalocaudal	180μ	180μ	180μ	170μ	184μ
Mediolateral	150	120	140	150	125
Dorsoventral	100	100	70	80	175
Diameters of opening into cup—					
Cephalocaudal	110	120	140	110	40
Mediolateral	120	100	120	110	....

The above measurements show how much alike in size and shape are these auditory pits. Measurements given by Van den Broek for the embryos he describes, of 22 somites,

show little increase in length or width of the cups, but there is a remarkable increase in depth and a very much more constricted opening to the exterior, showing how rapidly the cup is becoming converted into a vesicle.

THE NERVOUS SYSTEM.

The nervous system is in the stage where closure has just occurred and is complete, except for the anterior and posterior neuropores. The fusion of the lips of the neural groove is not very heavy and over most of the hindbrain and again over a large extent of the yolk sac the seam has opened in both of the embryos studied. Careful study of the sections shows, however, that there had been fusion, ragged edges being evidence of this, as is also the fact that the ectoderm is broken, and not continuous with the walls of the neural canal, as it would be if fusion had not yet occurred.

The anterior neuropore (plate 1 and plate 3, fig. 5) is not situated exactly at the most anterior point of the head, but on the surface just ventral to this, so that it looks ventrally as well as forward. It is situated in a shallow depression and is very wide open and looks directly into the cavities of the optic vesicles as well as into the lumen of the rest of the forebrain.

The posterior neuropore represents the still unformed, or at least undeveloped, portion of the spinal cord, and is wide open. It will be described later.

It will be seen thus that the nervous system is still open both in front and behind at the neuropores, but closed everywhere else. In Low's (1908) embryo, Pfannenstiel III, of 14 somites, a large part of the nervous system is still open in front, so that quite an advance in closure is shown by the embryos here described. Van den Broek's (1911) embryo of 22 somites and Thompson's (1907) of 23 somites show complete closure of the anterior neuropore. Embryo V and VI thus show a degree of closure which is coincident with their stage of development.

The nervous system conforms to the general contour of the dorsal surface of the embryo and exhibits one important flexure, the cephalic. The anterior part of the brain is flexed to form exactly a right angle with the rest, the flexure occurring in the region of the midbrain. In general contour and appearance the brain shows a remarkable correspondence to figs. 26 and 27 in the account of the nervous system in Keibel and Mall's Embryology. To make their figure serve here it would be necessary only to make a wider neuropore and indicate the neuromeres.

The anterior end of the nervous system, forming the brain, is divided distinctly into the three primary vesicles, each of which in turn shows a series of secondary divisions, forming the anlagen of many future structures in the brain (plate 3, fig. 5). These anlagen are in the form of the total folds, as described by Broman (1896) and Mrs. Gage (1905). By a total fold I mean one involving the whole brain wall and indicated by a bulging of the exterior coincident with an enlargement of the lumen, and bounded by furrows externally, which form corresponding ridges on the interior of the wall.

The forebrain (plate 3, fig. 5) as a whole is narrow from side to side and very deep in its dorsoventral diameter. Its lumen is narrow and slit-like. There are five distinct regions delimited in the forebrain, as follows:

The first is the optic evagination. This involves nearly the whole dorsoventral extent of the lateral wall of the brain just behind the anterior neuropore. There is yet no differentiation into optic stalk and optic cup, and the whole evagination is flattened so that its lumen is a vertical cleft, which opens in its whole dorsoventral extent into the lumen of

the rest of the forebrain. The optic evagination does not reach quite to the ectoderm and there is no evidence of any lens thickening.

The second forms the cerebral hemispheres. Above and behind the origin of the optic evagination, and involving the roof of the forebrain, is a small but distinct expansion, which is the beginning of the cerebral hemispheres. No evidence of the olfactory lobes are to be seen yet in front of the cerebral lobes, and this is probably to be associated with the presence of the still open neuropore, as this lobe is demonstrated by Mrs. Gage (1905) in a somewhat older embryo where the neuropore is closed.

The third division of the forebrain corresponds with what Mrs. Gage calls the infundibular fold. It is in exactly the same position as figured by her and is distinctly cut off by furrows from adjacent parts. It is situated immediately below and extends behind the optic evagination, involving thus the floor and lower part of the lateral wall of the forebrain.

Also involving the floor is the fourth fold, the hypophyseal, forming that part of the pituitary body derived from the brain. It occurs immediately in front of the cephalic flexure and is thus the furthest caudal portion of the floor of the forebrain. It is a distinct median evagination containing a small tubular lumen and projects directly caudad, to lie just in front of the anterior end of the notochord (plate 1) and against the front end of the gut. No pouch of Rathke yet reaches it.

The fifth fold in the forebrain differs from the condition found by Mrs. Gage in this respect, that one fold here extends from the posterior part of the roof of the forebrain, obliquely downward and forward across the lateral wall, ending just above the hypophyseal and infundibular folds. This includes all the region which is found in the albicantial and the two diencephalic folds in the embryo described by Mrs. Gage. This fold is large and well marked—in fact is more developed than any other except the optic.

The midbrain (plate 1 and plate 3, fig. 5) is quite distinctly marked out and is quite in accord with the descriptions of it as found in other young embryos. It occurs at the region of the cephalic flexure and so is wedge-shaped, the apex being the floor or ventral surface and the base of the wedge being the dorsal surface of the brain. The midbrain is incompletely subdivided into two portions, an anterior and posterior on each side, by a shallow groove starting on the roof and passing half way down the sides, where it is lost. The folds formed thus foreshadow the formation of the corpora quadrigemina. In Mrs. Gage's case this division of the mesencephalon is much more marked.

The isthmus is not well marked and no constriction or lessened development are in evidence at this stage, as shown by the diameters.

The hindbrain (plate 1 and plate 3, fig. 5) or rhombencephalon is well developed and shows a marked degree of differentiation for an embryo so young, all the total folds described by Broman and by Mrs. Gage being readily identified. Four cranial ganglia on each side are also to be found, representing 5 nerves, the trigeminal, facial, auditory, glossopharyngeal, and vagus.

Of the cerebellum there is little evidence yet, that part of the hindbrain from which it arises being hardly differentiated. The fourth ventricle, however, is indicated, for the dorsal part of the lumen, especially in the posterior portion, is expanded, appearing lozenge-shaped on section, while the ventral part of the lumen is cleft-like throughout.

On the side wall of the rhombencephalon and involving the floor are found 7 neuromeres (plate 3, fig. 5) which agree accurately with those found in this region of the brain of early human embryos by Mrs. Gage and by Broman.

The first neuromere, immediately behind the isthmus, is small and only slightly marked out. It is wedge-shaped, the apex being placed ventrally. It includes in the apex a slight extent of the brain floor, not having been yet forced entirely on to the side of the brain by development of surrounding parts, as in Broman's case.

The second neuromere is very large and bulging and causes a marked swelling of the floor of the brain in this region, where it gives the first indication of the location of the future pons. This neuromere is wider ventrally than it is above, to accommodate itself to the neuromere on each side of it, which is wedge-shaped, with the broad end dorsal. Associated with this second neuromere is the Gasserian ganglion, which is quite large. It is connected to the neuromere, but peripherally does not give indication of the three divisions of the nerve.

The third neuromere is large, though not so large as the second. It still includes a share of the brain floor, while in the stage described by Broman this neuromere has been forced wholly on to the lateral wall. It agrees with Broman's case in being wedge-shaped, with the narrow end directed ventrally.

The fourth neuromere is very large and causes a bulging of the floor of the brain below the level of the third. Associated with this neuromere is the acusticofacial ganglion, the two parts of which are readily recognizable. The anterior portion, forming the facial ganglion, lies just in front and almost in contact with the anterior end of the otocyst. It is connected to the brain and peripherally extends (plate 1) right out into the second branchial arch, which is rather remarkable for an embryo of this age. The acustic ganglion lies directly behind and in contact with the facial and is fitted in between the otocyst and the wall of the brain. It is quite small.

The fifth neuromere is similar in shape to the fourth, being rather rhomboidal. No structures are connected with it, but the posterior half of the otocyst lies opposite to it, the anterior half being opposite the fourth neuromere.

The roots of the seventh and eighth cranial nerves are invariably found opposite and attached to the fourth neuromere, as described here, but the position of the otocyst seems to vary, being usually opposite the fifth neuromere, as seen in the embryos described by Broman (1896) and by Mrs. Gage (1905). In this case, however, approximately half of the otocyst is anterior to the fifth neuromere, being opposite the fourth, and in intimate contact with both the auditory and facial portions of the acusticofacial ganglion. In Keibel and Mall's Embryology (1912) the location of the auditory vesicle is placed opposite the fifth neuromere only. Of course the embryos I have referred to are all considerably older than the ones here described, so that there is plenty of opportunity afforded for a change in the relations from those found at this time.

The sixth neuromere and those back of it resemble very much the neuromeres of the spinal cord, and this posterior part of the medulla is indistinguishable from the cord except for one feature, which is the commencing formation of the fourth ventricle, as shown by the expanded dorsal portion of the lumen. Each neuromere from here back is similar and includes a section of the whole nervous tube, but is not marked on the roof, as this is not yet separated from the ectoderm. The sixth neuromere has connected with it on each side the ganglion of the glossopharyngeal nerve. This ganglion is fairly large and extends about half the distance toward the branchial arch with which it is to be associated.

The seventh neuromere has connected with it the ganglion of the vagus. This is not nearly as large or as distinct as the ganglion of the glossopharyngeal nerve, but is quite recognizable. The sixth and seventh neuromeres have been constantly associated with the

ninth and tenth cranial nerves, respectively, so that these findings are in full accord with those of other investigators.

The next two neuromeres are included by Mrs. Gage as folds 8 and 9 of the medulla oblongata. She finds them as dorsal pockets only of the neural tube, but in Embryo VI they include the whole tube. These two folds lie in the region of the first three pairs of somites, the neuromeres being opposite the intersegmental clefts. The origin of the accessory portion of the eleventh nerve is stated to arise from these neuromeres, but no evidence of this nerve is here present. The ganglion crest of the neuromeres is continuous with the ganglion of the vagus in front. There is no trace of the hypoglossal nerve, whose fibers must come from these neuromeres, as they lie opposite the segments later included in the occipital region of the skull.

Accepting the number of neuromeres in the rhombencephalon as 9, there are to be found 11 (plate 1) in the spinal cord, the last one being opposite the thirteenth intersegmental cleft. There is no line of demarcation between brain and cord. The condition of the cord changes slowly and very gradually, becoming less in its various diameters as it is followed caudad. Back of the last neuromere it gradually becomes circular in section. In front of this it is much elongated dorsoventrally. At the level of the last somite the cord becomes open dorsally, forming the posterior neuropore. The walls are at first close together and the gutter formed is narrow and deep, but this gutter gradually becomes shallower and wider and finally, in the tail region, all trace of the lips of the neural groove are lost and the nervous system terminates as a flat plate which rapidly blends with the tissues of the primitive streak. Shortly before this fusion, from the under surface of the medullary groove to the notochord, the remains of the neurenteric canal pass, evident as a solid cord of cells, already described (plate 1 and plate 2, fig. 10).

The whole extent of the nervous system on its dorsal surface is still fused to the ectoderm; nowhere is there as yet any separation. In all the closed portion of the tube in the region of the spinal cord the neural crest is evident and from it there passes a spinal ganglion (plate 1) between every two somites as far back as the last neuromere. Back of this point no ganglia are yet evident. There is a neural crest also in the posterior part of the hindbrain, from which the ganglia of the glossopharyngeal and vagus nerves are formed. This crest seems to be directly continuous with that of the spinal cord and would thus agree with the views of Dohrn (1901), who found them continuous.

No motor nerves are yet in evidence in any portion of the nervous system.

Histologically the whole closed portion of the nervous system appears similar. There is an internal limiting membrane lying next the lumen, then the layer of ependymal cells. External to this is the mantle zone, in which the cells are apparently in the indifferent stage. Outside of this again is the marginal zone, formed of protoplasmic processes of the cells and containing absolutely no nuclei. This zone is not developed in the dorsal and ventral portions of the tube, but is well marked in the lateral regions. There is no division yet into the dorsal (or alar) and the ventral zones, corresponding to the sensory and motor regions of the cord. Inclosing the whole nervous system throughout is a very definite, thin, structureless, external limiting membrane. The nuclear layers in the walls of the neural tube vary from 4 to 6 in number.

The nervous system of Embryo V is so similar in every way to that of its twin, Embryo VI, that no separate description of any part is necessary, and it can be dismissed with only a few remarks regarding some slight individual differences. The appearance on section of the various parts of the brain and cord is almost identical in the two embryos. Embryo V,

however, does not exhibit quite as well developed a neural crest and series of spinal ganglia. It does possess trigeminal, acusticofacial, and glossopharyngeal ganglia of approximately equal development to its twin, and also exhibits the extremely large extension of the facial ganglia into the second gill arch. No vagus ganglion can be distinguished in Embryo V, and it will be remembered that this ganglion in Embryo VI was small, and though quite recognizable would easily be overlooked without careful search, so that this difference is not of great significance. The only other difference worth mentioning is that shown in the combined fold representing the albicantial and diencephalic folds as described by Mrs. Gage. As in Embryo VI, one fold only is found, in place of the three Mrs. Gage mentions, and this fold is most prominent. It stands out in a winged fashion on each side of the forebrain, and is even much more conspicuous than in its twin. Its posterior boundary is formed by a very deep groove, and this is the main factor in making the fold so prominent, as the posterior or caudal wall stands out perpendicularly to the wall of the rest of the forebrain. This fold is not so sharply delimited in front, because from the crest of the fold the anterior or cephalic wall slopes gently forward and is much longer than the other.

Apart from the differences mentioned above, there is complete agreement between the stage of development and the appearance of the nervous system of these two embryos, and no further description is necessary for the second.

Regarding the question as to what point is the morphological anterior end of the brain, I find valuable evidence here in support of the views advanced by Johnston (1910) that it is situated at the recessus præopticus. For a discussion of the various views on this question I refer the reader to the descriptions of embryos by Mrs. Gage (1905) and by Van den Broek (1911). It is sufficient to state that His (1893) and others have placed the extreme cephalic end of the ventrimesal line or basilar axis of the brain at a point on the anterior wall of the recessus infundibuli. The dorsimesal line is marked, of course, by the fusion of the lips of the neural groove. According to His, the side walls of the brain unite in front, forming a closing seam between the ends of the dorsimesal and ventrimesal lines. This occurs by the closure of the anterior neuropore. Most investigators have discarded the view of His regarding this closing seam and Mrs. Gage says "it logically follows the cephalic end is the point where the dorsimesal and ventrimesal lines meet." All writers seem to agree that this point does not coincide with the location of the anterior neuropore and of the part of it which longest retains its connection with the ectoderm. Stress is laid, however, on the presence of a seam as one means of identifying the dorsal surface. Now, in both of the embryos here described, the nervous system is nowhere separated yet dorsally from the ectoderm, so that there is no doubt of the location and extent of the dorsal seam. At the anterior end of the body the anterior neuropore lying between the optic vesicles is still wide open and is, as shown by the rolling of its lips out into the adjacent ectoderm, the still open portion of the dorsal seam. Nowhere have I seen any account of the closure of the nervous system in which it is stated to begin in any place except over the hindbrain and upper part of the spinal cord, whence it extends both caudad and cephalad. No closure begins at the cephalic end of the brain to meet the main closure, although the anterior neuropore does not always close regularly from behind forward. It is reasonable, however, to take the extreme cephalic end of the neuropore as the extreme front end of the dorsimesal line. This point, then, will mark the extreme front end also of the ventrimesal line or basilar axis, and it is situated in front of the origin of the optic vesicles and forms the preoptic recess. According to His and to Mrs. Gage and others, that part of the brain wall from the preoptic recess back to the infundibular recess is dorsal. If so, in these

young embryos it ought to give evidence of a seam, but no evidence whatever of any seam or fusion is to be found in this part of the brain. It does not seem reasonable to consider this region a part of the dorsal wall of the brain, when in all its relations it is so different from all the rest of the dorsal portion of the nervous system, and at this stage of development it also seems to me quite rational to take the presence of the seam at the line of fusion of the lips of the neural groove and the connection with the ectoderm as a criterion for determining what is the dorsal surface. Otherwise one is forced to the conclusion that the extreme anterior end of the brain closes very early and independently of the ordinary closure, the anterior neuropore being the space temporarily existing until these two regions of closure fuse. If this is the case this anterior end must close very much earlier, indeed, than the rest, for it is already separated by mesoderm from the ectoderm. The conclusion does not seem a reasonable one to me, and I also do not see any reason why, at this early stage of development, any part of the roof of the brain should be rotated down until it lies in line with the floor. The brain at this stage is a simple tube with dilatations representing the anlagen of its various parts, but there are no structural peculiarities that would indicate a displacement of the anterior end of the roof to the ventral surface. I think there is every ground to assert with Johnston (1910): "Rather, as the neural plate rolls up, the neural tube tapers to a point in the preoptic recess, and the lamina terminalis is the anterior part of the seam of closure along the mid-dorsal line."

CONCLUSION.

In conclusion I wish to briefly call attention again to the following points: These embryos are twins and show appearances and degrees of development which are almost identical throughout. Yet these embryos are not identical or "real" twins, as shown by the fact that they were not contained in one sac, but each embryo had its own individual membranes. These twins, therefore, are the product of the fertilization of two ova simultaneously or with only a very small interval between. This gives an opportunity for more variation than is possible with twins which are the product of one ovum, and produced by independent development of each cell of the 2-celled stage into an embryo. Yet in spite of this they show a remarkable correspondence. Two embryos more alike would be hard to find.

It is to be emphasized that these embryos are extremely valuable in bridging the large gap existing between embryos described to date, with 14–15 pairs of somites, and those of 22–23 pairs. That there may be no hesitation in accepting the work embodied in this paper, I can positively assert that there is no evidence or hint of any pathological condition in these embryos. They are in excellent condition for topographical work, but minute histological work on the cells can not be pursued on account of the slight damage resulting from the section cutting and from the unavoidable beginning of maceration before the embryos were extruded from the uterus. This damage, however, in no way interfered with the study of the form and relations of the various organs and parts of the body.

As my final word I wish to tender to Professor J. Playfair McMurrich my most sincere thanks for the loan of these valuable embryos and for furnishing me with material and all available facilities for prosecuting this study. It would be unfitting to close without also referring to his live, keen interest in the progress of this work and his pleasure in the results it has been my fortune to attain.

JUNE 1, 1914.

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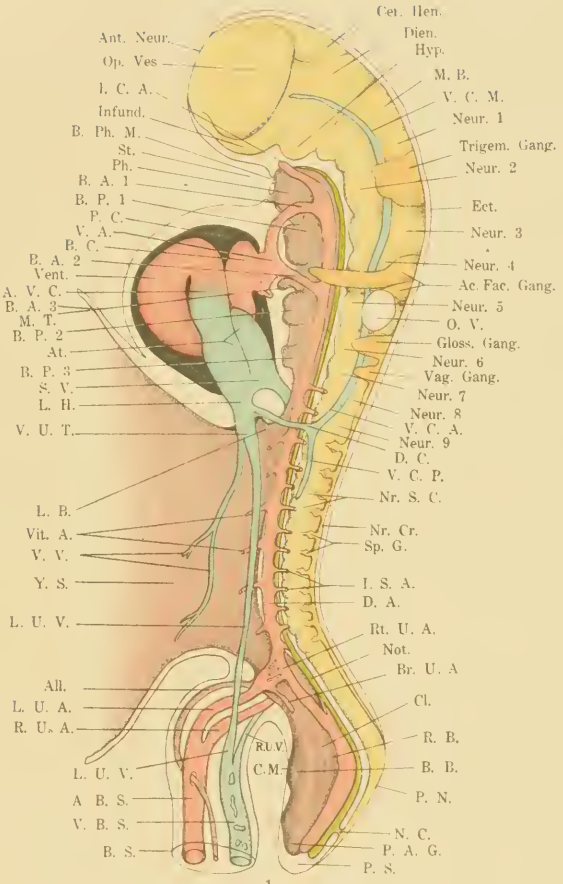
LIST OF ABBREVIATIONS USED IN ILLUSTRATIONS.

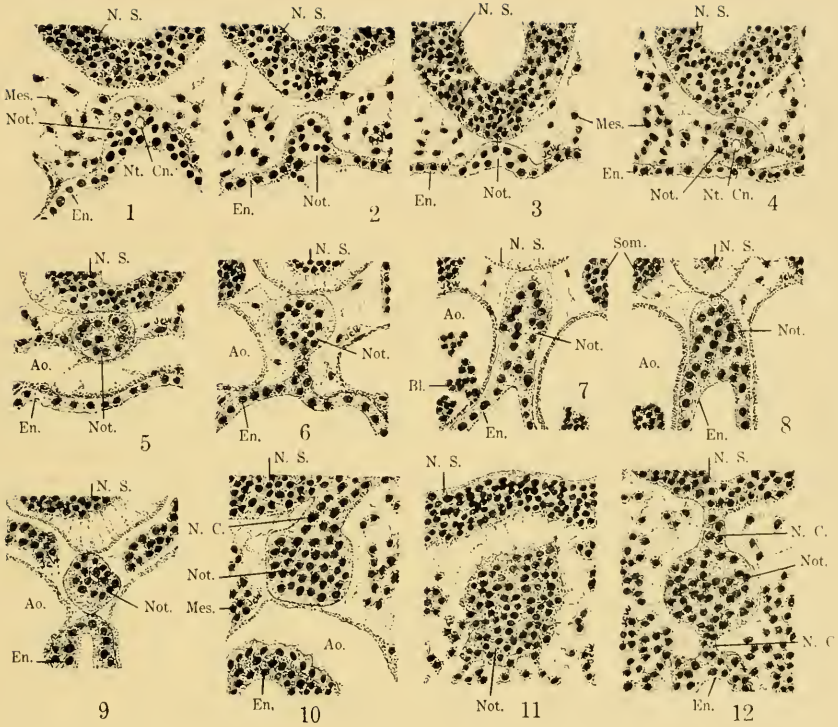
A. B. S.	Arterial blood sinus.
Ac. Fac. Gang.	Acusticofacial ganglion.
All.	Allantois.
Ant. Neur.	Anterior neuropore.
Ao.	Dorsal aorta.
Ao. P	Aortic process of sclerotome.
At.	Atrium of heart.
A. V. C.	Atrioventricular canal.
B. A. 1	First branchial artery.
B. A. 2	Second branchial artery.
B. A. 3.	Third branchial artery.
B. B.	Bladder bay of cloaca.
B. C.	Bulbus cordis of heart.
B. P. 1	First branchial pouch.
B. P. 2	Second branchial pouch.
B. P. 3.	Third branchial pouch.
B. Ph. M	Buccopharyngeal membrane, with perforations.
Br. U. A.	Branch of umbilical artery.
B. S.	Belly stalk.
Cav.	Cavity of somite.
Cer. Hem	Cerebral hemisphere.
Cl.	Cloaca.
C. M	Cloacal membrane.
Coel	Cœlom.
D. A	Dorsal aorta.
D. C	Ductus Cuvieri.
Derm.	Dermatome of somite.
Dien.	Diencephalon.
D. M.	Dorsal mesocardium.
D. R.	Degenerative remains of tubules.
Ect.	Ectoderm.
En.	Endoderm.
Fus. E	Fusion of ectoderm to branchial pouch.
Fus. N.	Fusion of notochord with cloaca.
Gloss. Gang.	Glossopharyngeal ganglion.
Gr.	Groove on cloaca marking rectum from bladder.
H. G.	Hind gut.
Hyp.	Hypophysis cerebri.
I. C. A	Internal carotid artery.
I. C. M	Intermediate cell mass.
Infund	Infundibulum.
I. S. A	Intersegmental artery.
L. B	Liver bay.
L. H.	Left horn of sinus venosus.
L. M. G	Lower myotomic groove.
L. U. A	Left umbilical artery.
L. U. V	Left umbilical vein.
M. B	Midbrain.
Mes.	Mesenchyme.
M. T.	Median thyreoid.
M. V.	Mesonephric vesicles.
My.	Myotome of somite.
N. C.	Remains of neurenteric canal.
N. Cd.	Nephrogenic cord.
Neur. 1-9	Nine neuromeres of hindbrain.
Not.	Notochord.
N. P.	Notochordal process of sclerotome.
Nr. Cr.	Neural crest.
Nr. S. C.	Neuromeres of spinal cord.
N. S.	Wall of central nervous system.
Nt. Cn.	Notochordal canal.
Op. Ves.	Optic vesicle.
O. V.	Otic vesicle.
P. A. G.	Postanal gut.
Pc.	Pericardium.
Ph.	Pharynx.
P. N.	Posterior neuropore.
Pn. T.	Pronephric tubules.
P. S.	Primitive streak.
P. V. A.	Paired ventral aortæ.
R.	Remains of pronephric tubules.
R. B.	Rectal bay of cloaca.
R. H.	Right horn of sinus venosus.
Rt. U. A	Roots of umbilical artery.
R. U. A.	Right umbilical artery.
R. U. V.	Right umbilical vein.
R. V. A	Right ventral aorta.
Scl.	Sclerotome of somite.
Som.	Wall of mesodermic somite.
Sp. G	Spinal ganglion.
St.	Stomodæum.
S. V	Sinus venosus.
Tr.	Trichter or nephrostome.
Trigem. Gang.	Trigeminal ganglion.
U. M. G.	Upper myotomic groove.
U. V.	Umbilical vein.
V. A.	Median ventral aorta.
Vag. Gang	Vagus ganglion.
V. B. S.	Venous blood sinus.
V. C. A	Vena cardinalis anterior.
V. C. M.	Vena capitis medialis.
V. C. P	Vena cardinalis posterior.
Vent.	Ventricle of heart.
Vit. A.	Vitelline artery.
V. U. T	Vitello-umbilical trunk.
V. V.	Vitelline vein.
W. D	Wolffian duct.
Y. S.	Yolk sac.



1

A graphic transparent reconstruction of the whole of Embryo VI except the nephrogenic system and mesodermic somites which are shown in text figure 3.

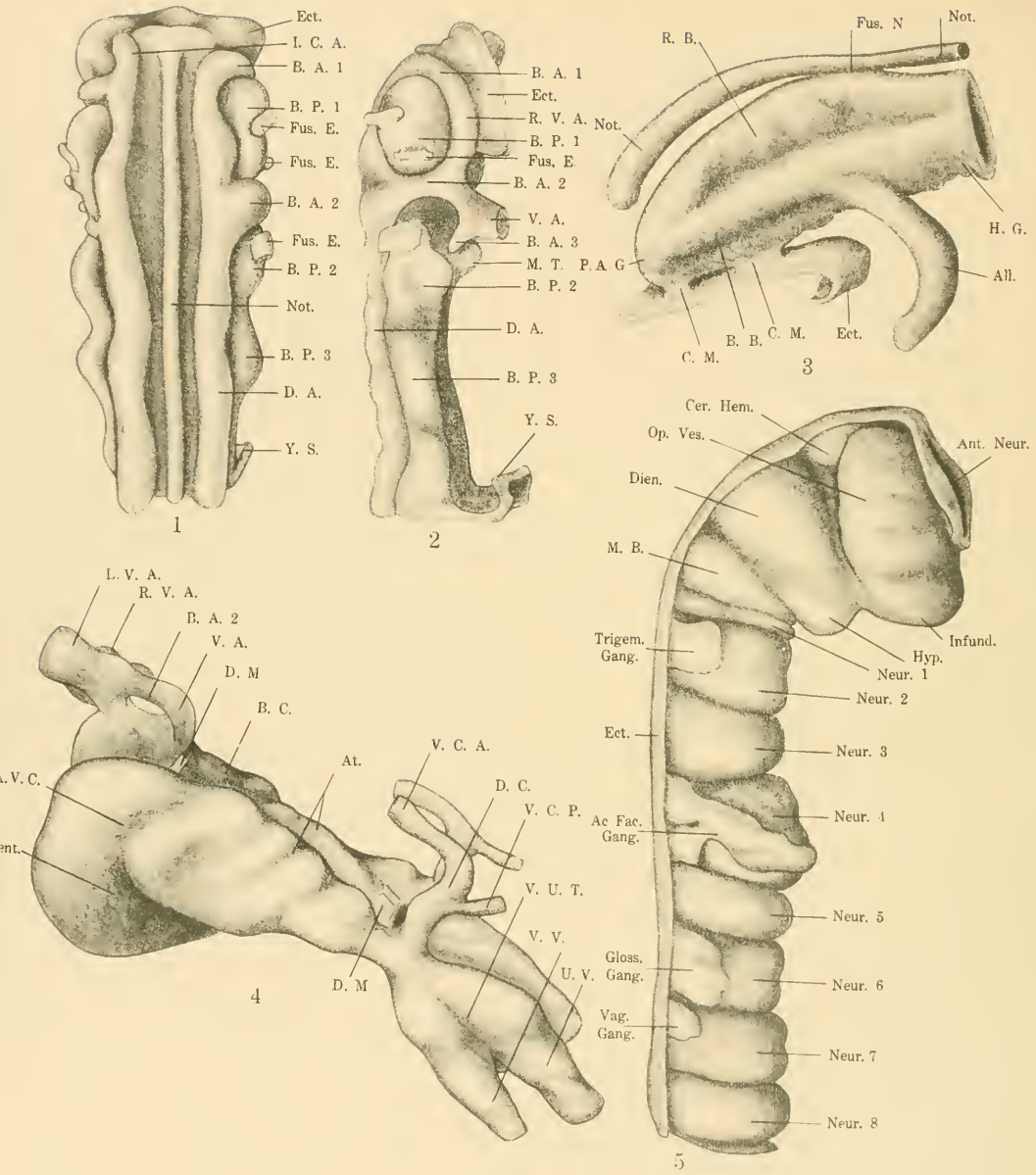
The arterial system is coloured red, venous system blue, alimentary system violet, notochord green, central nervous system light yellow, all ganglia and the neural crest orange yellow.



Figs. 1 to 11 are from Embryo VI; fig. 12 from Embryo V. All were drawn with the aid of the camera lucida. Magnification × 300.

Fig. 1. Notochord at its cephalic end. Notochordal canal is evident.
Fig. 2. Notochord at level of first branchial pouch.
Fig. 3. Notochord at level of second branchial pouch.
Fig. 4. Notochord at level of sinus venosus. Notochordal canal is evident.
Fig. 5. Notochord over middle of yolk sac. Dorsal aorta is shown under the notochord.
Fig. 6. Notochord at posterior end of yolk sac, connected by neck of cells to endoderm.
Fig. 7. Notochord over caudal end of hind gut.
Fig. 8. Notochord over beginning of cloaca.
Fig. 9. Notochord over cloaca at level of allantois.
Fig. 10. Notochord over level of caudal edge of cloacal membrane, showing remains of neurenteric canal.
Fig. 11. Notochord two sections before its fusion with the primitive streak.
Fig. 12. Notochord over cloaca in Embryo V, to show the remains of the neurenteric canal. Compare with fig. 10, from Embryo VI.

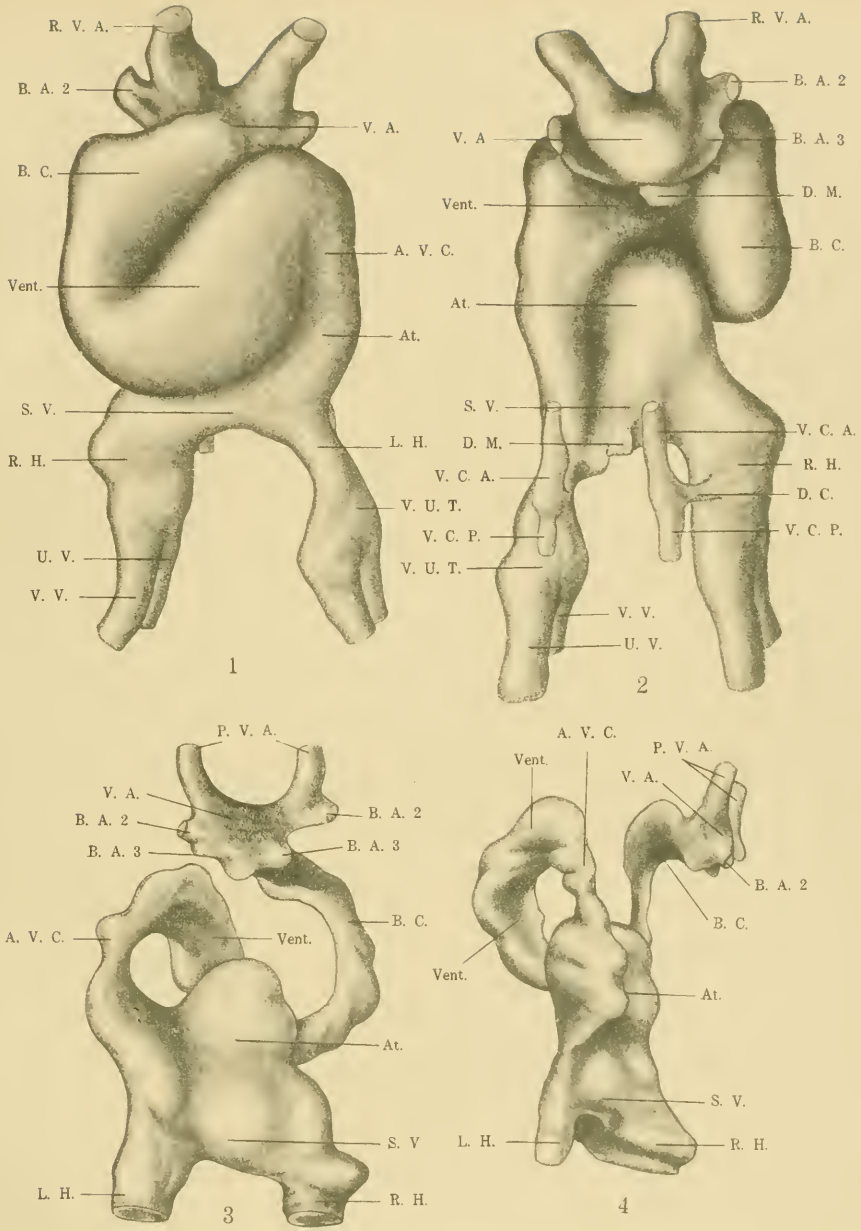
On page 40 will be found a list of abbreviations applicable to all the plates in this paper.



WATT del.

1. Dorsal view of wax-plate reconstruction of the pharynx in Embryo VI.
2. Lateral view of wax-plate reconstruction of the pharynx in Embryo VI.
3. Lateral view of wax-plate reconstruction of the cloaca in Embryo VI.
4. Lateral view, from the left, of wax-plate reconstruction of the muscular tube of the heart in Embryo VI.
5. Lateral view, from the right, of wax-plate reconstruction of the brain in Embryo VI.

For abbreviations see page 40



J. C. WATT del.

1. Ventral view of wax-plate reconstruction of the muscular tube of the heart in Embryo VI.
2. Dorsal view of wax-plate reconstruction of the muscular tube of the heart in Embryo VI.
3. Dorsal view of wax-plate reconstruction of the endothelial tube of the heart in Embryo VI.
4. Lateral view, from the left, of wax-plate reconstruction of the endothelial tube of the heart in Embryo VI.

For abbreviations see page 40

CONTRIBUTIONS TO EMBRYOLOGY, No. 3.

AN ANOMALY OF THE THORACIC DUCT WITH A BEARING ON THE EMBRYOLOGY OF THE LYMPHATIC SYSTEM.

By Eliot R. Clark,
Professor of Anatomy, University of Missouri.

AN ANOMALY OF THE THORACIC DUCT WITH A BEARING ON THE EMBRYOLOGY OF THE LYMPHATIC SYSTEM.

By Eliot R. Clark.

The case which is to be described has an exceptional interest, both because of its rarity and because of the bearing which it has on the still unsettled problem of the mode of development of the thoracic duct. It occurred in a dissecting-room subject, in a negro female (No. 3408 in the dissecting-room series of the Johns Hopkins Medical School), aged 39 years, of slight build, distinctly below the average in height, weighing only 102 pounds, whose death was due to "tuberculosis" (a diagnosis borne out by the condition of the lungs noted in the course of dissection). Thanks are due to Miss Goldman, Mr. Amberson, and Mr. Banks, without whose careful dissection and cooperation the report of this case would not have been possible.

Attention was first drawn to the lymphatic system by finding, during the dissection of the lower neck and axilla, a number of lymphatic vessels which were unusually distended by a whitish coagulum. One of these vessels, larger than the others, extended down into the axilla, where it received branches from numerous enlarged lymph glands. The duct extended beyond the axillary glands, in the direction of the thoraco-epigastric vein, in the subcutaneous tissue of the lateral body wall. At about the level of the sixth intercostal space the duct was cut across, in separating the fascia at the dividing line between the two dissection fields, before it had been found that there was anything unusual about the lymphatics. At the cut end the diameter was still considerable, and it was remarked at the time that this vessel was very much larger than could be accounted for by the lymph coming from the axillary glands alone. Anteriorly the duct joins the left subclavian vein in the angle formed by this vein with the internal jugular. Near the opening a second, smaller lymph duct was found, joining the subclavian. A search was made before the thorax was opened for the terminal portion of the thoracic duct and a fine vessel was seen in the usual position for the end of the thoracic duct, but was broken during the dissection.

Somewhat later, Mr. Amberson, dissecting the lower left thoracic and abdominal wall, traced a supposed subcutaneous "vein" from the lateral thoracic region posteriorly over the abdominal wall, and over the ligamentum inguinale (Poupart's) into the superficial fascia of the femoral triangle. To his great surprise he found that ducts led from the inguinal lymph glands into this supposed "vein"—that, instead of a vein, he had been following a greatly enlarged lymph duct. The case now became one of much interest; from the size of the duct it was suspected that it must drain at least a part of the abdominal viscera. Fortunately the thoracic and abdominal viscera had not yet been disturbed, so that it was possible to dissect here the main lymphatics.

The duct which had been followed along the lateral thoracic and abdominal wall was first studied. (Fig. 2, M. L. D.) It is a substantial vessel, which is duplicated posteriorly and anteriorly by smaller vessels. The middle undivided part consists of a stretch, 10 cm. long, starting from a point 14 cm. from the ligamentum inguinale, where it receives the posterior duplicating vessel. (Fig. 2, P. D. L.) The main duct has a marked widening above the ligamentum inguinale. Below the ligament its diameter is about 2.2 mm., while 3 cm. above the ligament its diameter is approximately 4.0 mm. This diameter

diminishes very gradually until, at a point 22 cm. from the ligament, it is reduced to approximately 2.0 mm. The main continuation anteriorly maintains this diameter of 2.0 mm., while the anterior duplicating vessel is about half as large. The cervical portion of the duct again widens until, at a distance of 3 cm. from its junction with the subclavian vein, it has a diameter of approximately 4.0 mm. The terminal portion, for about 1.0 cm., is distended with blood. The origin of the posterior duplicating vessel was not determined, as it was broken off during dissection. From the angle at which it joins the main vessel, and from the fact that, like the main vessel, it has a decided widening to 3.5 mm. at a corresponding place, there is little doubt that it took origin from lymphatic vessels in the inguinal region. All of the vessels were opened, in order to study the valves. In the main duct there is a valve, 1 cm. posterior to the ligamentum inguinale, a second valve 11.5 cm. anterior to the ligament, and a third above the point where the anterior duplicating vessel is given off. All the valves have the flaps directed so as to permit the lymph to run in an anterior direction. Between these three valves the inner wall of the duct is smooth. In the posterior duplicating vessel there are two competent valves, one in the widened region a short distance anterior to the ligamentum inguinale, and the second shortly below its junction with the main duct. The flaps of the valves are directed anteriorly. In addition there are numerous transverse thickenings which project into the lumen. In the anterior duplicating vessel a valve is present shortly beyond its origin from the main duct, its flaps directed anteriorly.

Unfortunately direct connection between the duct found in the body wall and the upper part, leading through the axilla to the subclavian vein, was, as has been explained, not seen. But, in view of the condition of the visceral lymphatics, to be described, there can be little doubt that they were continuous.

On dissecting the thoracic and abdominal viscera the following conditions are found: In the mid-thoracic region a miniature thoracic duct is present in its usual position between the azygos vein and the aorta. (Figs. 2 and 3, TH. D.) At no part of its course does its diameter exceed three-fourths of a millimeter. On being followed anteriorly it is found to pursue the usual course, crossing to the left and coursing toward the junction of jugular and subclavian veins. As already noted, the connection with the vein was lost early in the dissection. Posteriorly it grows smaller, and at the ninth thoracic vertebra it comes to an end by curving sharply to the right behind the azygos vein and by passing out into the ninth intercostal space in company with the ninth intercostal artery and vein. No trace whatever could be found of a continuation further posteriorly of this miniature duct. Two or three minute tributaries were found joining the duct along its course. Careful dissection ventral, dorsal, and to the left of the aorta failed to reveal a possible left thoracic duct.

As to the condition of the deep veins, the azygos vein presents a marked abnormality. First, it should be noted that the azygos and aorta lie rather further to the left than usual, so that the azygos, in the mid-thoracic region, is situated nearly in the midline. The usual one or more tributaries which cross the midline, dorsal to the aorta in the mid-thoracic region, carrying the blood from the hemiazygos, are absent. Instead, the left intercostal spaces, beginning with the fourth, are drained by veins collecting in a common trunk which runs posteriorly as far as the body of the ninth vertebra. This trunk is joined by a vein which runs from the left renal vein (fig. 3, A. L. V.), and receives the upper lumbar and lower intercostal branches. This vein represents a much widened ascending lumbar vein, continuous with the lower part of the hemiazygos vein. The common branch formed by these two veins is a trunk of considerable size, about 5.5 mm. in diameter, which crosses the

midline ventral to the aorta, at the level of the ninth intervertebral disk, to become the chief tributary of the azygos. (Fig. 3, CONN. v.) In fact, this branch is larger than the posterior continuation of the azygos itself, which is about 4 mm. in diameter. The azygos narrows rapidly below the point of junction of this branch, receiving branches from the tenth and eleventh intercostal and the subcostal spaces. A narrow vessel runs from the end of the azygos, across the body of the twelfth vertebra, dorsal to the aorta, and anastomoses with one of the left subcostal veins.

The vein mentioned, which runs from the left renal vein to join the left azygos, courses on the bodies of the vertebræ to the left of the aorta, and dorsal to the left renal arteries. It has a minimum diameter of about 2.7 mm.

Associated with this variation in the azygos veins is one of the left renal vein. This, instead of crossing the midline to the inferior vena cava, runs posteriorly, joining the vena cava at its origin opposite the angle formed by the two iliac veins. In addition to its connection with the inferior portion of the hemiazygos, the renal receives, as usual, the adrenal and ovarian veins.[1] The right renal vein is not abnormal.

To return to the lymphatics, it may be said at once that the abdominal and pelvic viscera, the intercostal spaces posterior to the ninth, and both posterior extremities are drained by lymphatics which collect into the left subcutaneous duct already described. (Figs. 2 and 3.) Following this duct backwards, it is found that, after passing superficial to the ligamentum inguinale, it runs posteriorly as far as the junction of the great saphenous vein with the femoral vein. It winds around the saphenous, as this vein passes through the deep fascia to join the femoral, and starts anteriorly along with the deep vessels. It soon divides, smaller branches passing superficial to the external iliac vessels, and running to the iliac lymph nodes which surround the external iliac vessels. The largest branch passes anteriorly at first medial to the external iliac vessels. A little above the ligamentum inguinale it winds around behind (dorsal to) the iliac vessels, until it lies lateral to the anterior third of the common iliac artery and vein. Here it divides into several branches, which pass in part to the more anterior iliac lymph nodes, in part anteriorly along the left of the aorta to the left lumbar nodes, and in part ventral to the aorta to drain directly the plexus surrounding the superior mesenteric artery and celiac axis.

The lymphatics, draining the abdominal and pelvic viscera and legs, reach the duct as follows: Several ducts from the left inguinal nodes join the main duct and its branches both before and after it curves around the saphenous vein. Others pass under the ligamentum inguinale to the lowest external iliac nodes. The lymph from the right leg, after passing through the right iliac nodes, is carried by a number of ducts, some of which run across the front of the sacrum and the last lumbar vertebra to the left iliac nodes, while others pass anteriorly on all sides of the iliac vessels, the lateral ones running to the right lumbar nodes, the ventral and medial ones running in part to a large node which lies ventral to the aorta just before its division, whose efferents pass to the left iliac nodes and in part dorsal to the aorta and vena cava, curving to the left and entering the left inferior lumbar nodes and the anterior iliac nodes. From the pelvic viscera ducts pass to the right and left iliac nodes, the right nodes being drained by the ducts already described.

The abdominal lymphatics present an interesting condition. There is no definite receptaculum chyli, nor are there any especially widened vessels in the region where the receptaculum is usually found. Instead there are plexuses and numerous narrow vessels lying dorsal to the aorta and vena cava inferior on the bodies of the last thoracic and all

[1] It should, perhaps, be noted that a double ureter is present on the left side; the left kidney is considerably longer, slightly narrower, but nearly twice as thick as the right, so that as a whole it is decidedly larger than the right.

four lumbar vertebræ.[1] The most anterior of these reaches the body of the eleventh thoracic vertebra. The widest of these vessels is but 2 mm. For the most part they are vessels running from the right lumbar nodes across to the left side, to the left lumbar nodes, or to ducts which pass directly to the left iliac nodes. Some ducts from the plexus, opposite the last thoracic and first lumbar vertebræ, however, wind around the left of the aorta and reach the plexus around the celiac axis and superior mesenteric, which drain the intestines, stomach, and in part the liver. It is quite probable, therefore, that some of the lymph from these organs passed through the plexus which lies in the position of the receptaculum chyli.

The most anterior part of these lymphatic plexuses consists of a loop which passes from the right lumbar chain, anteriorly, as far as the division of the azygos vein. (Figs. 2 and 3, A.) Here, ventral to the azygos, it bends sharply to the left, and, running posteriorly, ventral to the aorta, passes to a gland lying to the left of the aorta, opposite the twelfth thoracic vertebra. It is to be noted that this loop reaches nearly to the level at which the rudimentary thoracic duct ends. The two are here separated by the anomalous azygos connecting branch (fig. 3, CONN. V.), which is crossing from left to right, ventral to the aorta. No trace of a connection could be found between the two lymphatics by the most careful dissection.

Ventral to the aorta there are, in addition to the large lymph node over the bifurcation, two long, flattened nodes lying posterior to the place of origin of the renal arteries (fig. 3). These two nodes are connected with the node over the bifurcation by several vessels running along the aorta. They receive, also, vessels which course across the inferior vena cava, a vessel of considerable size which follows the vena cava as far as the diaphragm, vessels from the plexus around the celiac axis and superior mesenteric artery, vessels from the duodenal region and from the right lumbar glands. The two glands are connected with one another by several vessels. From the left of these two preaortic glands there is a glandular projection which passes dorsally to one of the left lumbar glands. From the left gland two vessels of considerable size run posteriorly, to the left lumbar and left iliac glands.

The vessels connecting the right lumbar chain of nodes with one another are less numerous than the corresponding vessels on the left side. Vessels were traced from the right chain to the tenth and eleventh intercostal spaces. On the left side, small vessels were found from the tenth and eleventh intercostal spaces which led to ducts passing posteriorly to the left lumbar nodes. A curious condition was found in the region of the twelfth rib. A lymphatic loop distended with a whitish coagulum lies to the left of the body of the eleventh vertebra and on the neck of the twelfth rib. It is connected with a considerable lymphatic plexus lying to the left of the aorta, which, in turn, is connected with the plexus around the superior mesenteric artery and celiac axis. To the left of the aorta there is a group of lymph ducts, in part interrupted by the left lumbar nodes and in part running free of them, which starts anteriorly with the vessels mentioned draining the tenth and eleventh intercostal spaces, and extends to the iliac nodes. This group receives most of the vessels lying on the bodies of the vertebræ, the left renal and left ovarian lymphatics, and most of the vessels lying ventral to the aorta, including connections with the lymphatics from the intestines, liver, and stomach, which follow the celiac axis and superior mesenteric artery. Some of the ducts pass dorsal and some ventral to the renal arteries. In this region they form a plexus which is interwoven with the plexus of sympathetic nerves. Small vessels from this chain were traced to the pillars of the diaphragm, presumably draining some of the diaphragmatic lymphatics. From the inferior end of the left lumbar nodes a

[1]Only four lumbar vertebræ are present in this subject.

stream of ducts leads to the left iliac nodes. The large node already referred to, which lies ventral to the aorta near its bifurcation, receives (in addition to the vessels mentioned) ducts from the vessels accompanying the inferior mesenteric artery.

In brief, then, the conditions present are these: The thoracic duct is rudimentary; it occupies its normal position, but extends posteriorly only as far as the body of the ninth vertebra, where it starts as a small vessel draining the ninth intercostal space. The dorsal body wall posterior to the ninth intercostal space, the abdominal and pelvic viscera, and both posterior extremities are drained by vessels which collect into a large duct which starts in the region of the anterior iliac lymph nodes opposite the last lumbar vertebra, runs posteriorly beneath the ligamentum inguinale, hooks around the terminal bend of the great saphenous vein, and then courses anteriorly in the superficial fascia over the ligamentum inguinale, over the lateral abdominal and thoracic wall, through the axilla, and into the left subclavian vein near its juncture with the internal jugular.

Associated with this condition is a variation of the hemiazygos and left renal veins, significant features of which are: (1) the veins draining the left intercostal spaces, below the third, collect into a vein which crosses to the right ventral to the aorta, at the level of the ninth thoracic vertebra, to join the main azygos, and this cross branch lies between the lower end of the thoracic duct and the most anterior loop of the abdominal lymphatics; (2) there is a considerable anastomosis between the hemiazygos and the left renal which, in turn, runs posteriorly to join the inferior vena cava at its point of formation by the junction of the two iliac veins.

So far as I have been able to learn, no such abnormality of the lymphatic system has been described.

While any explanation of this condition must necessarily be mainly speculative, certain facts, in connection with our knowledge of the mode of development of lymphatics, are suggestive. First, it should be noted that there is no evidence of any pathological condition in the region where the thoracic duct ends. Turning then to the embryo, it has been shown by Miss Sabin (**1**, 1913, 63) that, in pig embryos, valves begin to develop in lymphatic vessels in embryos of 7 cm. Thus, she was able, in embryos of 5.5 cm. (**2**, 1904, 86), by inserting the injecting needle into the dermis at any point, to inject the entire network of subcutaneous lymphatics, which form, at this stage, a richly anastomosing network over the body wall. In human embryos Miss Sabin (**3**, 1912, 728) found that valves apparently begin to develop in the larger vessels of the subcutaneous network in embryos of 5.5 cm. For a considerable time previous to the development of valves, the body-wall plexus collects anteriorly into ducts which pass into the axillary region, posteriorly into ducts which pass into the depth in the inguinal region, and which eventually reach the receptaculum. Polinski (**4**, 1910) has demonstrated, in bovine embryos, a temporary lateral vessel which differentiates in the midst of the plexus in the lateral body wall. Mierzejewski (**5**, 1909) has found in chick embryos a transitory longitudinal vessel in the body wall which runs from the axilla along the lateral body wall over the pelvic region. Mrs. E. L. Clark, in a series of observations, soon to be published, and which she kindly permits me to refer to, on the circulatory conditions in the superficial lymphatics of living chicks, finds that the circulation in lymphatics starts very gradually and that, in early stages, slight disturbances may result in a complete reversal of the direction of lymph flow. Obviously, then, since there is a considerable period in which no valves are present, there is the possibility that were there any unusual condition which should offer a sufficient resistance to the flow of lymph through the thoracic duct, the lymph might make its way posteriorly in

the deep abdominal lymphatics, and, passing through the inguinal lymphatics to the superficial body wall, eventually reach the subclavian vein by way of the axilla. In the present case such an obstruction may well have been afforded by the anomalous condition of the azygos vein, for the line of division between the rudimentary thoracic duct and the lymphatics draining posteriorly occurs at exactly the place where the large connecting branch from the veins draining the left thoracic cavity crosses in front of the aorta. While this vessel appears relatively small in the adult, much too small, perhaps, to be considered sufficient to cause an obstruction to the flow of lymph, it should be remembered that in young embryos the veins are relatively enormous. Moreover, since the left renal vein runs posteriorly to the junction of the two iliacs, and since there is still a connecting vein of considerable size from the left renal to the lower branch of the left azygos, it is highly probable that for a considerable embryonic period this vein carried much of the blood from the left leg, left half of the pelvis, left kidney, and left lumbar region.

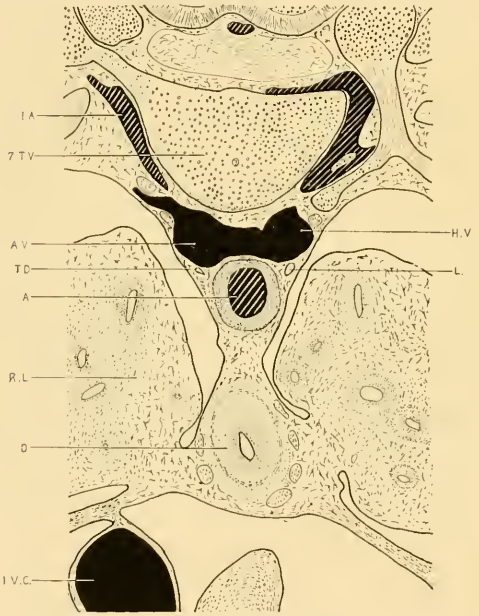


Fig. 1.

Transverse section through the region of the seventh thoracic vertebra of an injected human embryo (Carnegie Institution of Washington, Embryological Research, Collection No. 460, 21 mm. long, slide 26, row 1, section 4). The section passes through one of the anastomoses between the hemiazygos and azygos veins, passing, as it does normally, dorsal to the aorta. There is a lymphatic vessel on each side of the aorta, ventral to the azygos and hemiazygos veins respectively. The lymphatic on the right becomes normally the thoracic duct. Enlarged 38×. Drawn with camera lucida.

I. A., Intercostal artery.
7 T. V., Seventh thoracic vertebra.
A. V., Azygos vein.
T. D., Thoracic duct.
A., Aorta.
R. L., Right lung.
O., Esophagus.
I. V. C., Inferior vena cava.
H. V., Hemiazygos vein.
L., Lymphatic.

There is another possibility which should be mentioned: While the exact mode of development of the thoracic duct is not entirely settled, it is probable, as Miss Sabin (1, 1913) has suggested, that the anterior part is formed by the growth (in a posterior direction) of rudiments which have budded off from the veins in the neck, and that the posterior part is formed by the growth (in an anterior direction) of rudiments which bud off from the renal veins; that the two sets meet and anastomose, and eventually form the continuous thoracic duct. If such is the case, it is possible that the anomalous azygos branch has prevented the union of the two sets.

The actual conditions which are present in the normal human embryo are shown in figure 1, which represents a cross-section through the region of the seventh thoracic vertebra in an injected human embryo (No. 460, 21 mm., in the collection of the Carnegie Institution of Washington). The section shows the two azygos veins connected by a cross-anastomosis passing dorsal to the aorta. The relatively large size of the embryonic veins is obvious. In the angle between each azygos vein and the aorta there is a lymphatic vessel, the one on the right side being the early thoracic duct. It is easy to imagine the obstruction to the growth of lymphatics, which would be present, were the connection between the two veins ventral instead of dorsal to the aorta, especially in case the left vein and the connecting branch were much larger than in the section shown. Such a condition must have obtained in early embryonic stages in the case under discussion.

This case furnishes a most striking instance of the dependence of anatomical structure on mechanical factors. Out of the lymphatics of the subcutaneous tissue of the left body-wall, which ordinarily develop into narrow vessels draining in two directions, into the axilla and the inguinal region, with capillary or (at most) very narrow anastomosis, there has been produced a large vessel through which passed all the lymph of the posterior half of the body, while the thoracic duct, deprived of this drainage, is a minute vessel, hardly more than one-tenth its normal size, extending posteriorly only as far as the ninth thoracic vertebra. Moreover, along the course of this subcutaneous duct, anterior to the ligamentum inguinale, there is a definite widening, corresponding somewhat to the receptaculum chyli, which is missing. That blood-vessels are governed in their growth by mechanical factors has been shown by Thoma (**6**, 1893) who finds that an increase or decrease in the amount of blood-flow leads to increase or decrease in the size of the vessel, while an increase or decrease in pressure causes increase or decrease in the thickness of the wall. It is apparent that lymphatic vessels respond similarly to mechanical forces, since the passage of a large amount of lymph through an unusual route has led to the formation of a duct many times larger than the vessels normally present, while the diminution in lymph flow through the thoracic duct has been accompanied by a corresponding diminution in its size.

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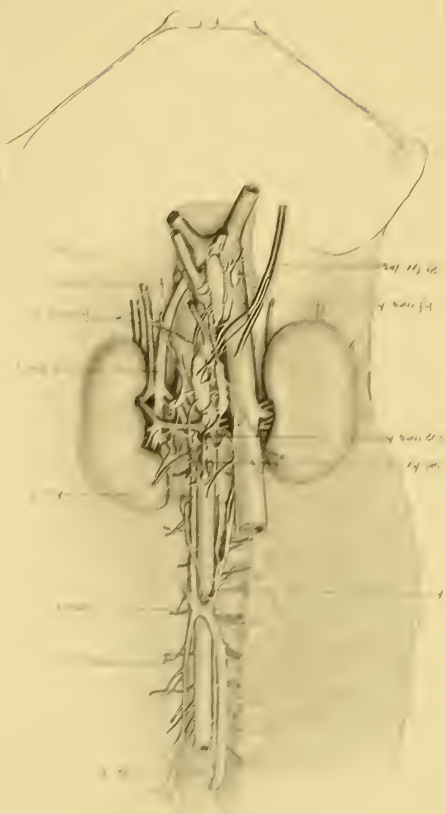
EXPLANATION OF FIGURES 2 AND 3.

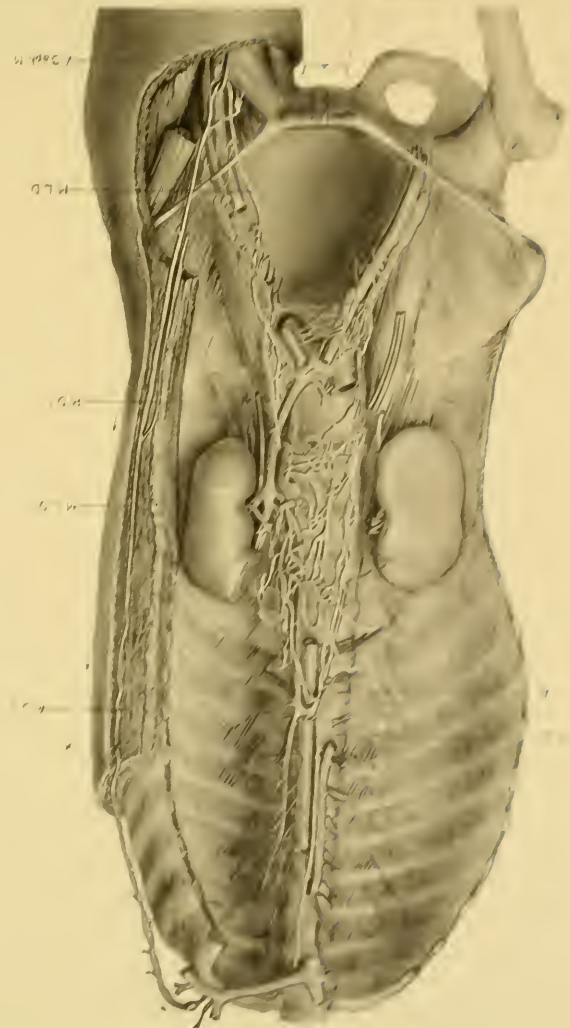
FIG. 2

Drawing to show the deep abdominal lymphatics, the thoracic duct, and the subcutaneous duct in the case described in the text. The inferior half of the aorta and the inferior vena cava are removed to show the plexus and glands lying on the bodies of the vertebræ. The azygos vein is cut and drawn back to show the ending of the miniature thoracic duct. The * shows the place at which the subcutaneous duct was divided early in the dissection. The anterior end of the left kidney is cut off to show underlying lymphatics. The arrows are opposite the place where definite valves were found in the subcutaneous ducts. A, most anterior of lymphatics of abdominal plexus. A V L, anterior duplicating lymphatic. M L D, main lymph duct. P V L, posterior duplicating lymphatic. TH D, thoracic duct, ending blindly anteriorly, where it was broken during dissection. V SAPH M, vena saphena magna. In the lumbar region several cut ends are shown of vessels which passed ventral to aorta and vena cava; the continuations of these vessels are shown in fig. 3.

FIG. 3

Drawing to show the abdominal lymphatics lying ventral to aorta and vena cava inferior. Their connections with the deeper lymphatics are shown as cut ends. The arrow indicates the beginning of the main lymphatic duct. Same as fig. 2. A L V, ascending lumbar vein, running from the renal vein to join with the hemiazygos vein (HEMIAZ.) to form the connecting vein (CONN. V.), which crosses ventral to the aorta to join the azygos vein (AZ. VEN.). L REN V, left renal vein. L OV VES and R OV VES, left and right ovarian vessels. CEL. AX, celiac axis. SUP MES A, superior mesenteric artery. INF MES A, inferior mesenteric artery. TH D, thoracic duct.





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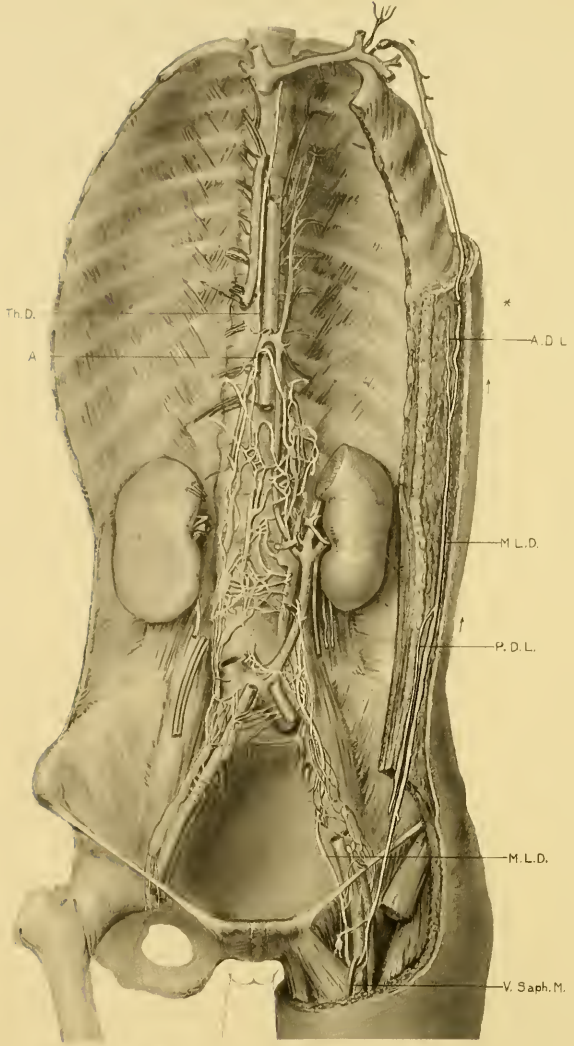
Th. D.
A
A. D. L.
M. L. D.
P. D. L.
M. L. D.
V. Saph. M.

Fig. 2

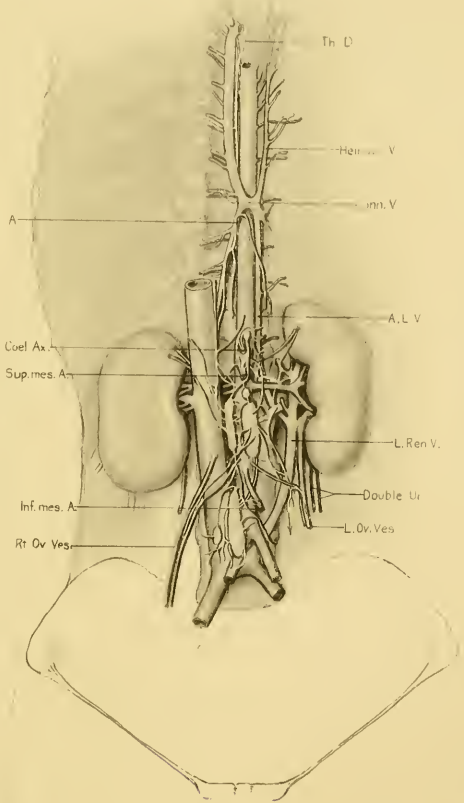
Th. D.
A
A. L. V.
Coel. Ax.
Sup. mes. A.
L. Ren. V.
Inf. mes. A.
Double Ur
L. Ov. Ves.
Rt. Ov. Ves.

Fig. 3

CONTRIBUTIONS TO EMBRYOLOGY, No. 4.

FIELDS, GRAPHS, AND OTHER DATA ON FETAL GROWTH.

By Arthur William Meyer,
From the Division of Anatomy of the Stanford Medical School.

FIELDS, GRAPHS, AND OTHER DATA ON FETAL GROWTH.

By Arthur William Meyer.

At the suggestion of Professor Mall and through the courtesy of Professor Williams I was enabled to obtain abstracts giving the fetal measurements, the duration of pregnancy, and such other data as might be desired from the case histories of patients from Professor Williams' clinic. As these abstracts were made more than half a decade since, they do not cover the entire material from the Department of Obstetrics of the Johns Hopkins Medical School, but only 4,530 cases. The immediate object of making these abstracts was the utilization of the data so obtained for the correction and, so far as might be, also for the extension of the curve of prenatal growth for length.

Since material from early abortions is comparatively rare among the cases ordinarily coming for obstetrical care, by far the largest part of the statistics covered the later months of pregnancy only. From the 4,530 abstracts, 2,476 were selected for the construction of graphs of growth. For this purpose the cases were usually plotted with duration in days as the abscissa and weight in grams or length in centimeters as the ordinate. However, on one chart weight in grams was used as the abscissa and length in centimeters as the ordinate. Other graphs were also formed to reveal the character and to illustrate the reliability of the data themselves. All plotting was done on a large and corresponding scale and cases falling at the same point of intersection were indicated by an Arabic numeral at that point. Although only 2,476 different cases were involved, approximately 12,000 plottings were done. The time-consuming nature of this work has been largely responsible for the delay in the compilation and analysis of the abstracts, the taking of which was a rather arduous task in spite of the careful way in which the histories are kept.

As is shown by reference to the original charted fields here reproduced, the graphs are medians and not averages. The most outlying cases were ignored, and those falling at different distances from the median were assigned equal value in its determination. Hence, all that these curves signify is that as many cases fall on the one side of the median as on the other, but not that most of the cases lie on it nor that the cases falling on it represent the average length or weight of the fetuses at that age. The empirical mode was not determined, except for birth, length, and for the occurrence of labor, as figures 5 and 6 show.

Although some of the outlying cases show clearly that there is occasional error (unavoidable no doubt) in some of the histories, it was thought best not to make corrections, since purely arbitrary criteria would have to be followed in making them. Besides, in so doing there is danger of eliminating all cases representing wide but entirely normal fluctuations. In the selection of the histories cases were included or excluded for plotting solely on the basis of the character of the histories themselves—sometimes the whole history—but only rarely, on account of the character of individual measurements, unless these had been called in question by those taking them or were brought in question by the subsequent history of the case to which they belonged.

Before proceeding to a discussion of the graphs a summary of the cases utilized will be given. This will convey a better idea of the character of the data used for graphical representation. The publication of the original charts as plotted also enables anyone to draw his own curves and conclusions and reveals any personal equation that may have intruded itself.

The average duration of pregnancy (as reckoned from the beginning of the last menstrual period, in all cases, with a duration of 236 to 329 days) was 279.8 days in the case of 1,186 Caucasians and 276.9 days in the case of 1,181 negroes. These averages agree very well with the story of the charts, although they are, of course, too low for full-term averages. Since the average duration of pregnancy for mature fetuses, as counted from the date of coitus, in a total of 2,578 cases reported by Ahlfeld, 1869 and 1871, Schlichting, Issmer, 1889, and Inouye, 1912, and those of Lowenhardt as well, was 269.19 days, a somewhat lower average duration than the normal could be expected in the series of cases concerned here. As will be seen later, the comparatively high average duration nevertheless obtained, which so closely approximates the normal, has undoubtedly resulted from the inclusion of histories with an erroneously long duration.

The average weight of 1,026 females with a duration of 236 to 320 days was 3,242.3 grams and that of 1,033 males was 3,387.4 grams, while that of 1,031 whites and 1,027 negroes was 3,436.5 and 3,185.4 grams respectively. The average length of the Caucasians falling in this period was 49.8 cm., that of the negroes 48.5 cm., and that of the females of both races was 48.7 cm. as compared to 49.6 cm. for the males.

The average weight of 1,146 males of both races of all ages *as plotted* was 3,258.4, and that of 1,161 females was 3,197.6 grams; although below the preceding averages (as would be expected) it is evident that both these averages are only slightly below the normal averages for the sexes as reported from some European clinics, in spite of the fact that my statistics include fetuses from 180 days on and that approximately half of them are negroes. Zangenmeister (1911) reports the average weight for 11,181 collected European cases as 3,242.49 grams and their average length as 49.93 cm. The average weight of all plotted cases of both sexes and races in this series was 3,228 grams. However, the averages for length for these plotted cases of all ages, which are 48.1 cm. for the males and 47.1 for the females of both races, are manifestly somewhat lower in comparison with the weight averages. It is interesting to observe that the differences between the average weight of the sexes in the charted cases of all ages is only 60.8 grams, although the difference in length is 1 cm., or fully equivalent to the sexual differences at birth. These Weissenberg (1911) gave as 0.8 cm., while Stratz (1909) regarded them as practically non-existent, and later (in 1910) as quite insignificant, in spite of the fact that he reported (1909) a sexual difference in natal weight of 250 grams as obtained from 400 cases. This sexual weight-difference far exceeds that of the usual European statistics.

From a comparison of these figures it is evident that the difference between the average weights of the sexes rises from 60.8+ to 157.1 grams merely by the exclusion of all cases with a duration of less than 236 days, and similarly, that the differences in average length rises from 1.0+ to 1.6+ cm. Moreover, it is also evident that the *percentage* sexual differences in both length and weight increase with advancing maturity, as might be expected.

Although I regret exceedingly that the data at hand did not enable me to determine how early these sexual differences are recognizable and when the greatest *percentage* sexual differences occur, yet it may be quite safely inferred, I think, that sexual differences in weight probably appear earlier than sexual differences in length. It would also be interesting to learn whether the advent of these differences can be correlated in any way—as seems probable—with special developmental changes in the ovaries and testis after the manner of the later adolescent differences and changes. However, the observation of Fesser (1873) that males are 77 grams heavier in the ninth than in the eighth month and that females are heavier in the eighth month, as well as the similar but somewhat contrary conclusions of Hecker, probably rest on too small and hence on a misleading basis.

Out of a total of 2,298 cases as plotted for weight 252, or 10.9 per cent, weighed over 4,000 grams, and of this number 154 were males and 98 females. Only 8 weighed over 5,000 grams, and of this number 7 were males and 1 a female, 6 were white and 2 black. The total number of cases which were 52 cm. long and over, out of a series of 2,307 of both races and sexes, was 415, or 17.9 per cent. Of these, 262 were males, 153 females, 287 white, and 128 black.

Of 2,092 cases with a given *duration of over nine months (252 days)* the heaviest was a white male 49 cm. long, with a duration of 261 days and a weight of 7,545 grams, but the longest, on the contrary, was a white female weighing 4,035 grams, with a duration of 287 days and a length of 59 cm. The shortest was a male negro measuring 21 cm., with a duration of 266 days and a weight of 2,920 grams. The shortest Caucasian was a female 40 cm. long, weighing 2,450 grams and having a duration of 275 days. The lightest of all cases was a white female, with a length of 41 cm., a duration of 256 days, and a weight of 1,295 grams. The heaviest negro was a female 52 cm. long, with 316 days duration and a weight of 5,556 grams. The longest negro was likewise a female, weighing 4,195 grams, with a length of 57.75 cm. and a duration of 306 days.

From these figures it will be seen that the fluctuations in weight amounted to 113.5 per cent of the weight of the lightest and 31.8 per cent of that of the heaviest. The shortest fetus, which was only 51.3 per cent as long as the lightest, nevertheless weighed 208.5 per cent of the latter. Similarly, the fluctuation between the shortest and longest fetuses was equal to 17.4 per cent of the former and 63.1 per cent of the latter.

It is interesting to compare the fluctuations in weight in these cases with those existing between twins of the same and of different pregnancies, even if the results in the one case can not be considered confirmatory of those in the other. Because peculiar circulatory conditions may exist in case of multiple pregnancy, one might expect to find greater variations in these cases, but such is not the fact in this series, at least. The greatest difference in the lengths of practically full-term twins (250 and 266 days) from the same pregnancy was 5 cm., or 11.6 per cent of the length of the shorter in two instances. The difference in weights between the individuals of these respective pairs was equal to 330 grams, or 14.9 per cent of the weight of the lighter in case of the younger pair of female twins and 690.4 grams or 30.4 per cent of the weight of the lighter of the older pair of male twins. However, these differences are not the maximum differences noticed between individuals of the same pair, for the length and weight of the male of much younger twins were 42 cm. and 1,680 grams respectively, and the corresponding measurements of the female were 36 cm. and 1,285 grams. Hence, in this pair the difference in length was 16.6 per cent of the length of the shorter and the difference in weight was 30.7+ per cent of that of the lighter.

The weight of the heaviest twin was 3,882.4 grams and that of its mate (which was also a female) was 3,402 grams. If we contrast with this the weight of the lightest twin over 252 days or 9 months old (which was 2,052 grams) and that of its female companion (which was 2,685 grams), we see that the difference in weight between full-term twins is 89.2 per cent of that of the lightest, while the greatest difference in length was 27.5 per cent of the length of the shortest, which was 40 cm. long. It is also interesting to note that the two longest twins, which measure 51 cm. each, are exceeded in weight by several which are only 44.5 cm. long. From these things it is evident that the fluctuation in the size of twins, at large, both in length and weight, is considerably less than in the case of single births. In the latter the maximum weight differences amounted to 113.5 per cent of the lightest as compared with 89.2 per cent in the case of twins. Similarly, the maximum differences in length amounted to 171.4 per cent of the length of the shortest in case of

single births, but only to 27.5 per cent in case of twins of different pregnancies and, of course, much less in case of twins from the same pregnancy. The existence of such exceedingly large and apparently normal fluctuations naturally necessitates the greatest caution in the use of any curve of growth for the determination of the age of a fetus even in the later months of pregnancy. It also enforces the necessity for a large basis if more than the roughest kind of approximation is to be attained in the construction and use of curves of growth. Moreover, it also justifies, it seems to me, the disregarding of far-outlying cases in the construction of graphs representing the median.

The above lack of correlation between weight and length recalls the observations of Bonnet (1884 and 1889) on ruminants, especially the sheep, and also those of Lomer (1889), who stated that it is surprising that two fetuses which may have the same length and weight, equally long fingers, and equally sized eyes and ears, may nevertheless not infrequently have hearts of wholly different size. Or, on the contrary, the fact that three fetuses whose body-weight varies by 1,000 grams may be found to have hearts of the same size and weight. As might be expected from this, Lomer found similar variations in all organs of the healthy fetal body. Moreover, it may be recalled that Oppel (1891) found the same thing true in a number of vertebrates and that Keibel (1894 and 1895) called attention to the occurrence of the same phenomenon in pigs.

In reflecting upon the possible explanation for these things one is naturally led to think of the internal secretions. As far as body-length and total weight are concerned the recent work of Cushing (1911) and others would seem to suggest a possible explanation for fetal gigantism or obesity. However, such an explanation could scarcely hold for individual organs, although there would, *a priori*, seem to be no reason why these could not be affected individually as well as individual portions of the osseous system or the whole of it. Although I do not wish to assume a causal relationship, I am also reminded in this connection that some years since I noticed that many of the sheep fetuses of the third month, even, with marked goiters, were very plump. However, since the basis of observation was very small, I could only conclude that this was probably nothing more than a mere coincidence.

Among the total 2,476 cases plotted—not all on any one chart—318, or 12.8 per cent, had a duration of 300 days and over. Hübner (1913) found only 498 cases, or 3.2 per cent, among a total of 2,000 births in Berlin with a duration of 302 to 324 days, while von Winkel found only 3.3 per cent with a duration of 302 to 347 days among 1,702 cases in Dresden. Of the above 318 cases 133 had a length of over 50 cm. or a weight over 4,000 grams. Among these 133 there were 68 males with an average weight of 3,797.5 grams and an average length of 52.6 cm., and 55 females with an average weight of 3,862.3 grams and a length of 52.2 cm. However, since only 55 of the 318 cases, or 17.2 per cent of those with a duration of 300 days and over, had a length over 52 cm. and only 42 or 13.5 per cent weighed over 4,000 grams, it would seem that the duration of pregnancy must have been inaccurate—*i. e.*, alleged too long—in quite a large percentage of cases. This assumption is also confirmed by the character of the right extremity of the curve in figure 1, but seemingly contradicted by the fact that Kaul (1912) found only 2.8 per cent of the new-born to weigh 4,000 grams and over in a total of 12,886 mature births at Breslau. Kaul also gives the following percentages of heavy births for the following clinics: Dresden 2.76, Munich 3.45, Bonn 4.76, Marburg 3.38, Leipzig 4.68, Kiel 8.31. The average percentage of heavy fetuses in full-term pregnancies for a total of 78,352 cases in these cities, as calculated from the figures given by Kaul, is 4.3.

Since as many as 252 cases, or 10.9 per cent, out of a total of 2,298 cases of all ages plotted in this series in figure 3, had a weight of over 4,000 grams, while only 14.2 per cent of those with a duration of over 300 days reached or exceeded this weight, it is evident that fetuses with this or a greater weight in our series among those with a duration of 300 days and over *were only slightly more numerous than among all cases plotted.* Kaul, on the other hand, found heavy fetuses 4.2 times as common among those with a duration of over 300 days than among births at large. Similar results were also obtained by others, for according to Hübner (1913), von Winkel found heavy fetuses 4 times as common and Hübner 3 times, among those with a duration of over 302 days, as among *full-term* births at large. It must also be emphasized in this connection that the percentage of heavy cases among this whole series of mature and premature cases is extremely large, especially, as we have seen, when compared with the European statistics. As stated above, the average for the latter is 4.3 per cent, which is only 42.6 per cent as many as in the Johns Hopkins series. That is, heavy fetuses are less than half as common among a series of 78,000 full-term European births as among 2,298 cases of both races with a *duration of 180 days and over* from the Department of Obstetrics of the Johns Hopkins Hospital. This disproportion in the frequency of heavy cases is all the more striking when it is recalled that half of the Johns Hopkins cases were negroes and that the presence of premature births of necessity considerably lowers the percentage of heavy ones. Moreover, the presence of such a large percentage of heavy infants might also be interpreted as confirming the accuracy of the histories, were it not for the fact that heavy infants among those with a duration of 300 days and over were but slightly more numerous than among all cases at large. It is true that Kaul found that only 37, or 11.7 per cent, of the heavy infants in a series of 12,886 cases had a duration of over 300 days, while in our series this is true of 14.2 per cent. Although Hübner does not give the number of cases, except for himself and von Winkel, he gives the following percentages of heavy fetuses with a prolonged duration as found by the following investigators:

Authority.	Per cent.	Duration of time (days).
Füth-Enge	15.7	From 302 to 351
Füchs	11.4	From 302 to 341
Gossrau	17.3	From 303 to 349
Hübner (397 cases)	9.8	Over 302
Do	11.9	Over 300
Jacoby	9.4	From 302 to 349
Starcke	14.7	Over 302
von Winkel (28,736 cases)	14.6	Over 302

Disregarding the slight discrepancy between the periods, the average percentage of cases with a duration of over 302 days (of these investigators) is 13.3. The slight difference between these percentages and ours could be disregarded were it not for the fact that the total list of premature and mature fetuses in the Baltimore series contains so many more heavy fetuses per 1,000 than the European. However, there seems to be a great difference in the frequency of heavy fetuses, for Inouye found only 0.93 per cent of heavy cases out of a total of 7,285 births, and it is interesting that all these percentages corroborate the well-known fact that many (Kaul puts it at 50.4 per cent) of the heavy fetuses with a prolonged duration were heavy before the end of the normal duration of pregnancy.

The large percentage of heavy fetuses in the service of Professor Williams also suggests the need for caution in the comparison of European with American anthropometrical statistics. One is tempted, to be sure, to suggest explanations for this decided difference in the ratio of heavy fetuses between Baltimore and the above-mentioned European cities, and no doubt someone will be reminded of Shroeder's humorous suggestion that his assistants must have exerted considerable tension on the legs of the new-born babies in order to get such a high ratio of long fetuses in his clinic. Nevertheless, I am certain that these differences can not be attributed to errors in the weighing. Besides, there are other much more plausible explanations.

A similar disproportion between the European and American statistics is present in the occurrence of cases weighing over 5,000 grams. During a period of 18 years at Breslau, in a series of 12,886 fetuses, Kaul reports, for example, the occurrence of but a single fetus weighing over 5,000 grams, while in this comparatively small series of 2,298 cases from Baltimore there were 8 with this weight or relatively 5.6 times as many, or 560 per cent. Moreover, Kaul's figures for Marburg, Leipzig, and München, covering 42,941 cases over a long series of years, give only 1 case over 5,000 grams in 3,303 births, or only 9.9 per cent as many as in our series. Kaul also says that during 11 years in the Dresden clinic not a single child was found to weigh over 5 kg. and adds that von Winkel found not a single case weighing over 6 kg. in an extensive series of 30,000 cases. Yet there is one case weighing 7,545 grams in this comparatively small series of 2,476 cases.

Among the 252 fetuses weighing over 4,000 grams there were 185 Caucasians and 64 negroes; 1 was a mulatto and 2 were unrecorded. Among the 42 births with a duration of 300 days and over and a weight above 4,000 grams, 30 were whites and 12 blacks, 25 males and 17 females. Only 34 of these 42 cases had a weight of 4,000 grams and over and also a length of 50.5 cm. and over. This would seem to imply that length must be set at practically the normal natal average if it is to be used *in conjunction with weight* in forensic medicine. Moreover, as will be seen, and as has often been stated, length alone is probably a far better guide than weight alone in the determination of the correctness of unusually long gestations.

Twelve of the above 34 cases were females and 22 males, and 25 belonged to the white race and 9 to the black. There were 123 cases or 27.1 per cent with a length of 51 cm. and over among those with a period of 300 days and over. Of these, 68 were males, 55 females; 83 whites, 39 blacks, and in 1 case the race was not given. Among the total 2,476 cases plotted, 453 were 52 cm. long and over, but only 299 or 66 per cent of these were *more than* 52 cm. in length. Of the latter, only 55 or 18.4 per cent had a duration of more than 300 days, and 74 or 24.7 per cent had a duration less than 280 days. Of those with the former duration, 123 or 27.1 per cent were 51 cm. long and over. Moreover, the 18.4 per cent of the cases which had a duration of more than 300 days constituted but 12.1 per cent of those 52 cm. long and over which were contained in the entire series of cases. Similarly, although only 14.2 per cent of the cases weighing over 4,000 grams had a duration of 300 days and over, 59 or 23.4 per cent of them had a duration of less than 280 days, leaving 62.4 per cent of the heavy fetuses as falling between 280 and 300 days. These percentages confirm the now generally accepted opinion, also emphasized by von Winkel and Zangenmeister, that heavy fetuses usually have a prolonged period of gestation. This is true of 76.6 per cent of the heavy cases in this series.

Out of the 453 cases 52 cm. long and over in a series of 2,476 cases, the sex was given in 415. Of these, 262 were males, 153 females; 287 were white and 128 black. Of the 55 over 52 cm. long, 26 were males and 29 females; 39 were Caucasians and 16 negroes.

Among the total number of 4,530 abstracted cases, there were 73 instances of multiple pregnancy which were composed of 71 cases or 1.6 per cent of twins and two cases or 0.04 per cent of triplets.

The graphs in figure 1 show the cases of a certain length in centimeter intervals from a length of 39 to 59 cm. inclusive in a series of 2,554 cases, from the Department of Obstetrics of the Johns Hopkins Hospital and from Hasse's 935 cases. The extremely close correspondence between the forms of these curves is striking and the only essential difference, aside from the great fluctuation in the number of fetuses in the 45 to 48 cm. lengths of Hasse's curve, which is undoubtedly due to the comparatively small number of cases, is that by

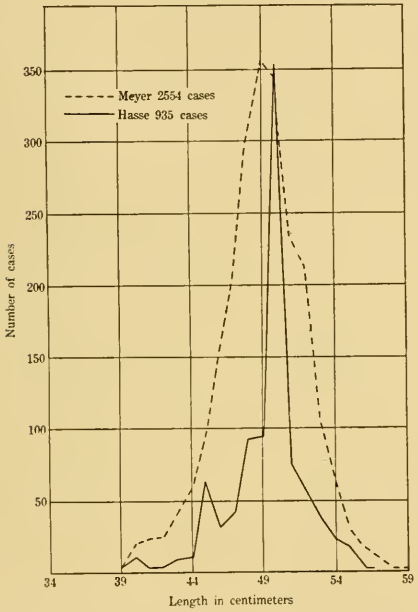

FIG. 1.

Graphs illustrating the number of cases for each centimeter's length from 39 to 59 cm. inclusive. Fractions of a centimeter, which were few, were counted with the nearest integer, the half centimeters going with the lower figure. Meyer 2,554 cases, Hasse 935 cases.

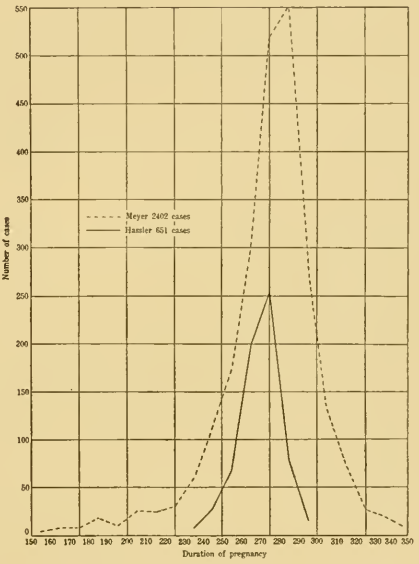

FIG. 2.

Graphs showing the number of deliveries in each 10-day interval from 150 to 340 days. Meyer 2,440 cases, Hasler 651 cases.

far the largest percentage of Hasse's cases were 50 cm. long instead of 49 cm. as in my series. The different location of the mode in my series is very evidently due to the fact that half of the cases from Professor Williams' clinic were negroes, and also to the presence of more immature cases. That is, 355 or 37.9 per cent of Hasse's cases are 50 cm. long, but only the same number of the present series of 2,311 cases, or 15.1 per cent, are 49 cm. long.[1]

On comparing these curves with those in figure 3, which are based on practically the identical material, the very sharp ascent to and descent from the maximum in the frequency curves for length and the gradual ascent to, and the still more gradual descent from, the maximum in the weight curves are very striking. Moreover, only 129, or 13.8 per cent,

[1]Curves based on percentages would have been preferable; nevertheless it hardly seemed of sufficient consequence.

of Hasse's cases fall in the most common weight interval of 3,250 to 3,500 grams, while 403, or 17.8 per cent, of the Johns Hopkins series fall into the most common but somewhat lower interval of 3,000 to 3,250 grams. Although the percentages in the most common weight interval in these two series are practically alike, Hasse found 37.9 per cent of his cases in a common length interval, as compared to 15.1 per cent in the Baltimore series. For this difference I can offer no explanation, except that the fluctuations tend to increase with the number of cases, although hardly to the degree here indicated, and that methods of measurement may to some extent be responsible. Moreover, in contrast to Hasse, the percentages in the common intervals of length and weight of our series differ but slightly—by only 2.7 per cent. As might be expected, this difference is to the advantage of the weight interval, which is a comparatively larger interval and hence should include a relatively larger percentage of cases. The length interval of 1 cm. is manifestly only about 2 per cent of the average birth-length, while the weight interval of 250 grams, on the other hand, is approximately 8 per cent of the average birth-weight.

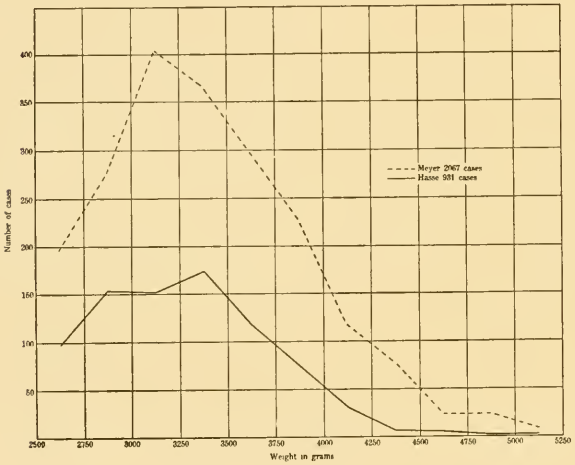

FIG. 3.

A graph similar to that in figure 4, giving the number of cases in each 250-gram interval from 2,500 to 5,250 grams inclusive. Meyer 2,076 cases, Hasse 931 cases.

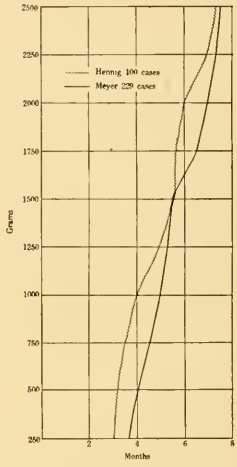

FIG. 4.

Graphs for weight of Hennig and Meyer. Hennig 100 cases, Meyer 229 cases.

The marked difference in the length and weight curves is due to the fact that in the case of weight several adjoining intervals contain almost as large a percentage of cases, but this is not true in case of the length intervals. This difference is also very noticeable indeed if the figures giving the number of cases in each centimeter length and each 250-gram interval are arranged in column form.

The curves in figure 2 give the number of deliveries in each 10-day interval from 150 to 340 days. Here the difference in position of the peak of the graph is due to the fact that Hasler's graph was based on duration as estimated from conception, while my graph is based on duration as estimated from the beginning of the last menstruation. Bearing this in mind the correspondence is excellent.

In figure 5 the number of deliveries per day are plotted, beginning with 260 days. The numbers above indicate the total number of cases for each day. Here, too, the large number of cases with a long duration is evident.

Figure 4 gives the curves of growth of weight of Hennig and myself. The former is based on 100 cases, the latter on 229. Neither is carried beyond 2,500 grams, because that is where Hennig's curve stops. The peculiar disagreement between these curves between a weight of 1,250 and 1,750 grams is puzzling. However, I am inclined to regard Hennig's curve as probably the more defective, for it is based on a comparatively much smaller number of cases and also because we know that a rapid increase in weight occurs between a weight of 1,300 and 2,300 grams. Nevertheless, the sharp increase and decline in my curve are probably also incorrect and due to a too narrow statistical basis.

Figure 6 represents various curves of length. Those of Toldt and Mall are drawn after Mall (1910), page 200. Here the close correspondence between the character and location of the curve of Hennig, that of Shroeder-Ahlfeld as given by Stratz (1909), which

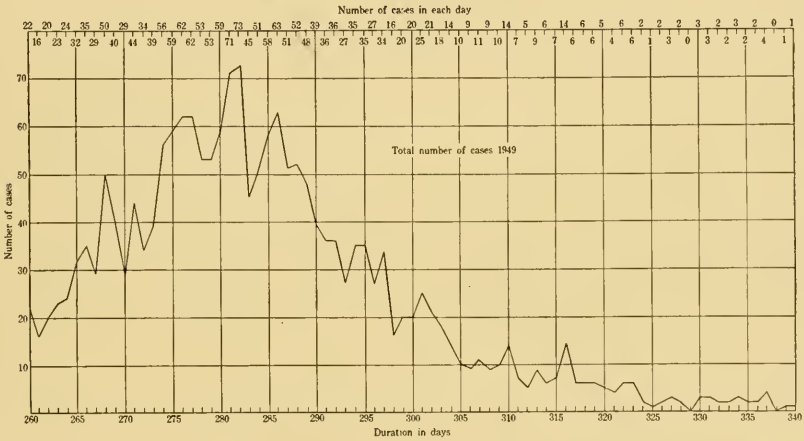

FIG. 5.

Number of deliveries daily between 260 and 340 days. The figures above represent the exact number of deliveries indicated on that point on the graph. 1,949 cases.

coincides with that of Stratz (1910), and my curve is evident. The fact that my graph lies to the left of all the others, including that of Hecker and Michaelis, is difficult to explain, except upon the assumption that the other curves were based on averages, while my curve is a median. Not that I assume a definite mathematical relationship between the average and median values; for as far as I can see it is impossible to decide in advance what their relation in a given case is. An inspection of the fields might help to suggest where both lie, but their exact location could be determined only by calculation. As far as Toldt's curve is concerned, his confusion of two measurements, as Mall (1907) pointed out, affects Toldt's curve in its lower segments only—below an age of $4\frac{1}{2}$ months—and can hence be ignored here in the comparison of my curve and Toldt's. However, since I suggested above that my series of cases included too many with a long duration, it may be urged that my graph should consequently be displaced to the right instead of to the left, where it is actually found. Nevertheless, I consider that this effect would be but a slight one and would not

compensate for the possible differences between the average and the median. The fact that my curve, which is based on 2,394 cases, does not reach 50 cm. until 282 days, may be due to the fact that it is lowered, especially in its highest portion near term, by the presence of cases with too long an alleged duration. Through a reduction in scale it has also become very regular. The rather marked inclination from the vertical at its upper extremity also

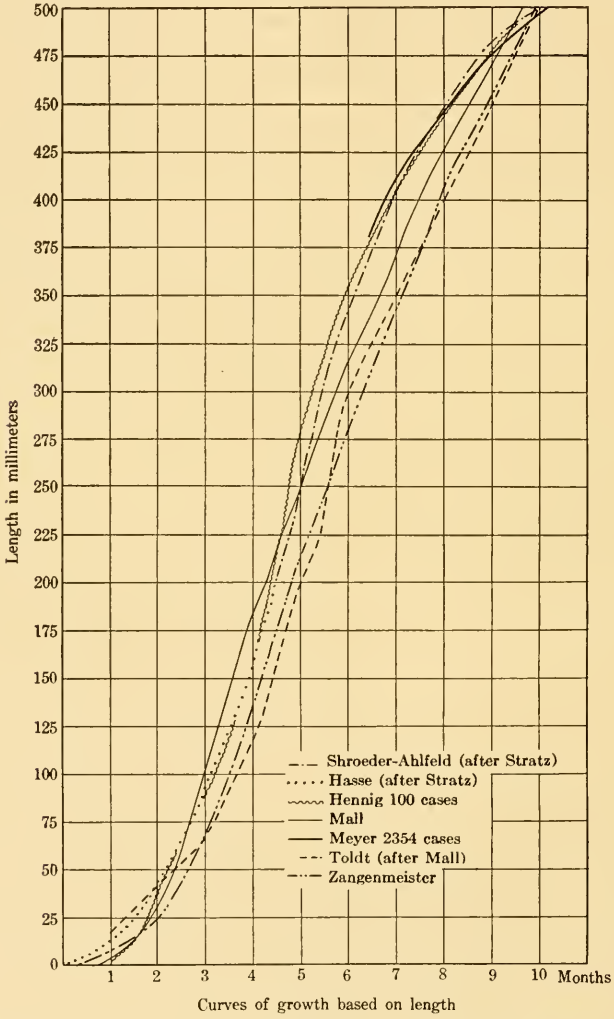

FIG. 6.

Graphs of Shroeder-Ahlfeld (Stratz) Hennig, Mall, Toldt, Zangenmeister, Hasse, and Meyer (partial) for length.

characterizes it and is in harmony with the decreased rate of growth in length observed at this time by Shroeder-Ahlfeld, and Hecker, and also by others.

An inspection of these curves shows that there is unanimity only regarding the starting-point of the curves, for they diverge somewhat even at term and for a large extent of their course they are separated by an interval of approximately one month. This is practically the amount of fluctuation assumed by Zangenmeister and Heuser in connection with their curves, and if we assume a similar range for curves in figure 6, then it is evident that the most outlying cases on this set of curves will be separated by a time interval of 2 months.

Figures 10 to 13 explain themselves, and for comment on them and on certain deficiencies in all curves of growth the reader is referred to the companion article on curves of prenatal growth and autocatalysis published elsewhere.[1] In this article, which is based on the same material, other aspects of the subject are discussed and figures with grouped curves and also others with curves abbreviated from the original charts are included.

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[1] Roux's Archiv, 1914.

DESCRIPTION OF FIGURES.

Fig. 1. Graphs illustrating the number of cases for each centimeter's length from 39 to 59 cm. inclusive. Fractions of a centimeter, which were few, were counted with the nearest integer, the half centimeters going with the lower figure. 2,554 cases Meyer, 935 cases Hasse.

Fig. 2. Graphs showing the number of deliveries in each 10-day interval from 150 to 340 days. 2,402 cases Meyer, 651 cases Hasler.

Fig. 3. A graph similar to that in figure 1, giving the number of cases in each 250-gram interval from 2,500 to 5,250 grams inclusive. 2,076 cases Meyer, 931 cases Hasse.

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Fig. 5. Graph giving number of deliveries daily between 260 and 340 days. The figures above represent the exact number of deliveries indicated on that point on the graph. 1,949 cases.

Fig. 6. Graphs of Shroeder-Ahlfeld (Stratz) Hennig, Mall, Toldt, Zangenmeister, Hasse, and Meyer (partial) for length.

Fig. 7. Graph based on length in centimeters and age in days. Both races and sexes, 2,436 cases from 10 to 59 cm. The cases represented by rings were added subsequently and were not used in locating the median. A portion of Mall's curve is shown in the lower left-hand corner as a solid line. The dotted portion of the curve is projected.

Fig. 8. Chart and graph based on weight in grams and duration in days. Both races and sexes. 2,298 cases, 100 to 5,000 grams in weight.

Fig. 9. Chart and graph based on weight in grams and length in centimeters. 2,274 cases. Both sexes and races.

Fig. 10. Graph for females based on length. 1,161 cases.

Fig. 11. Same for males. 1,146 cases.

Fig. 12. Same for negroes. 1,155 cases.

Fig. 13. Same for whites. 1,147 cases.

FIG. 7

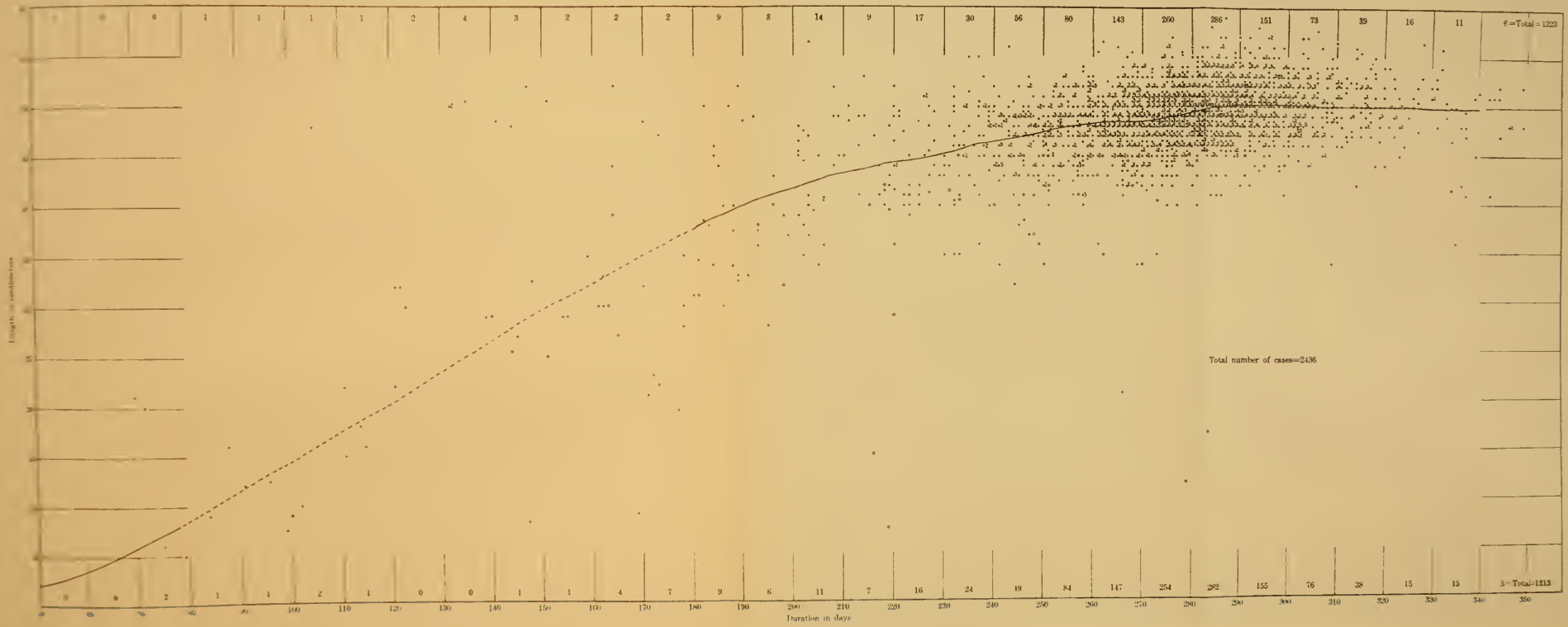
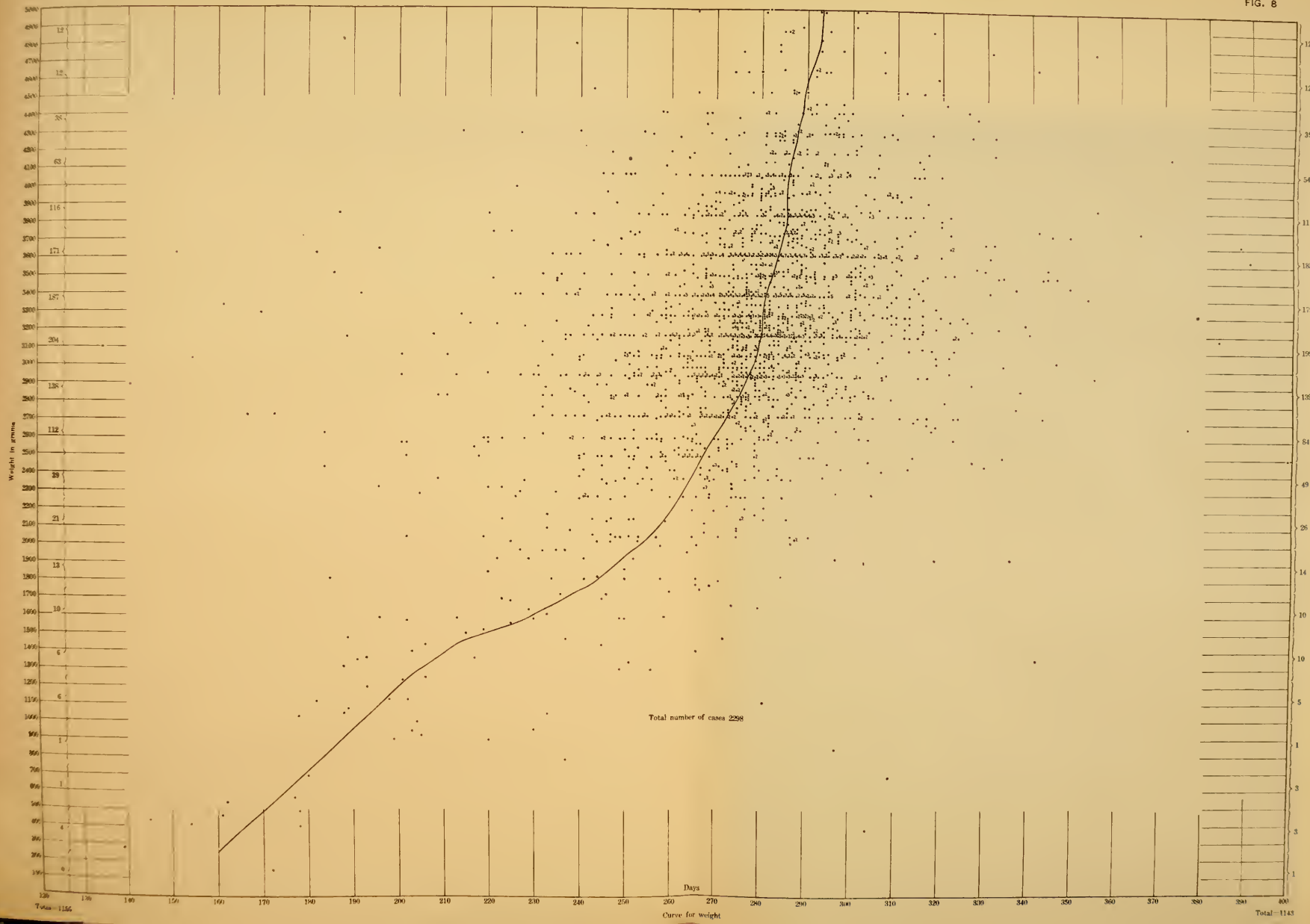

6=Total=1223
Total number of cases=2436
5=Total=1213
Duration in days

FIG. 8


Weight in grams
Days
Total number of cases 2298
Curve for weight
Total=1156
Total=1143

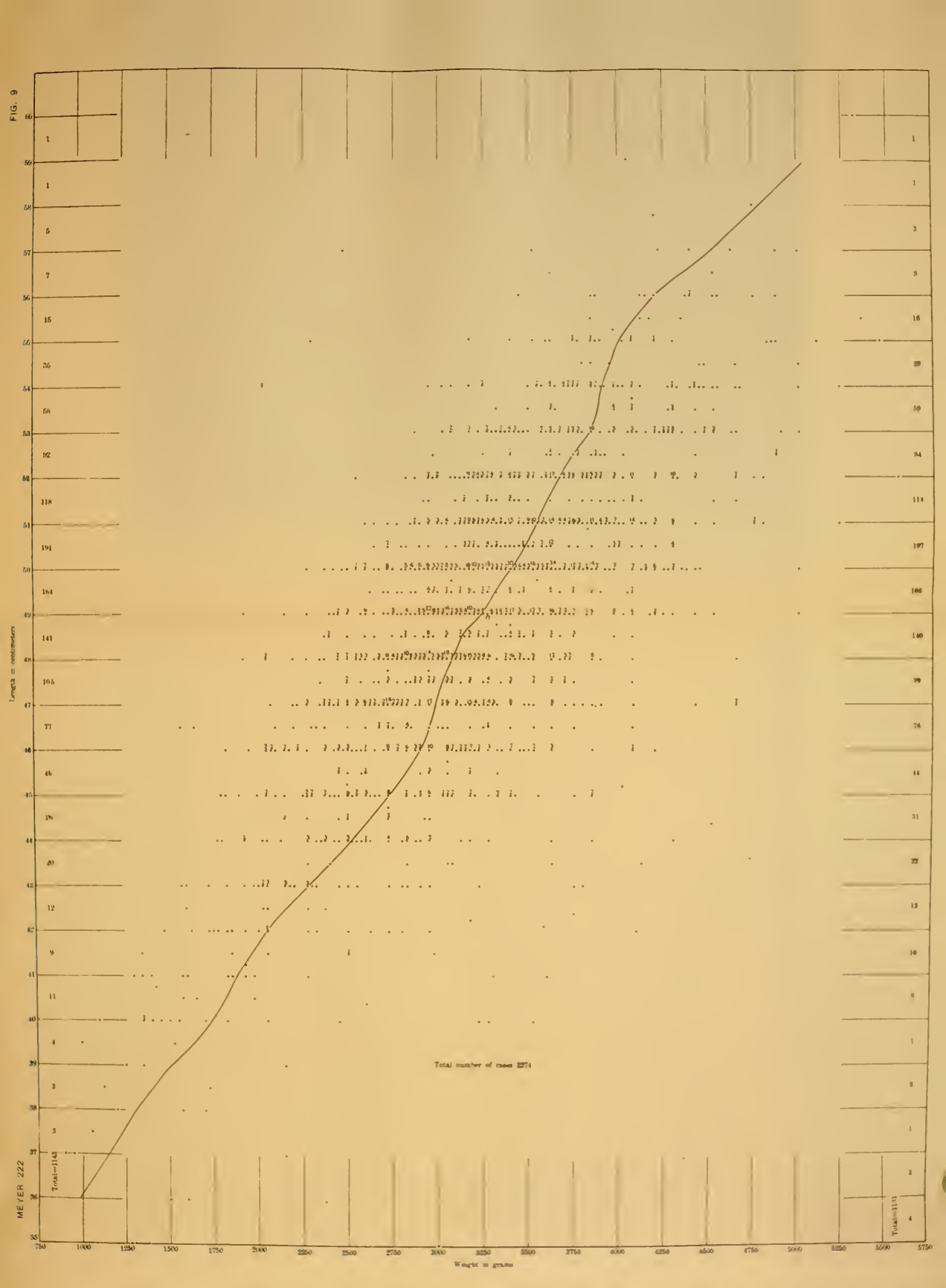


FIG. 9
MEYER 222
Length in centimeters
Weight in grams
Total number of cases 2274
Total=1143
Total=1131

FIG. 10

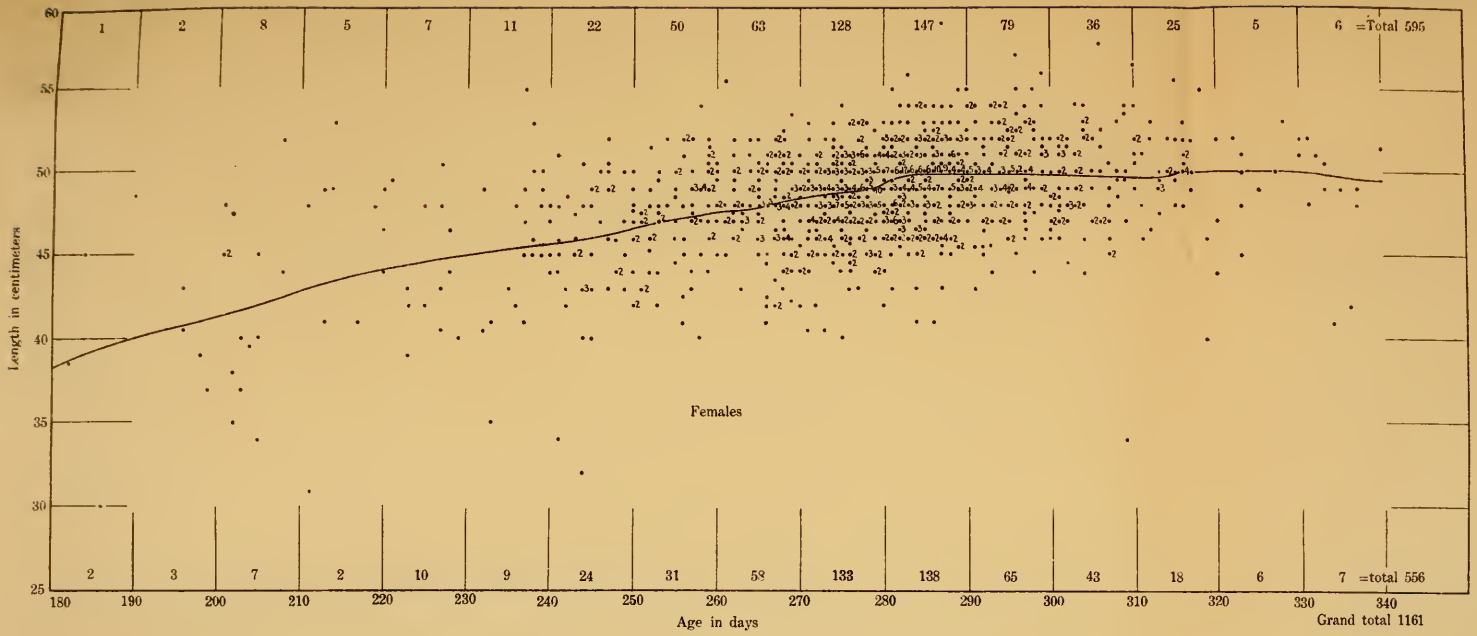

1 2 8 5 7 11 22 50 63 128 147 79 36 25 5 6 =Total 595
2 3 7 2 10 9 24 31 58 133 138 65 43 18 6 7 =total 556
Length in centimeters
Females
Age in days
Grand total 1161

FIG. 11

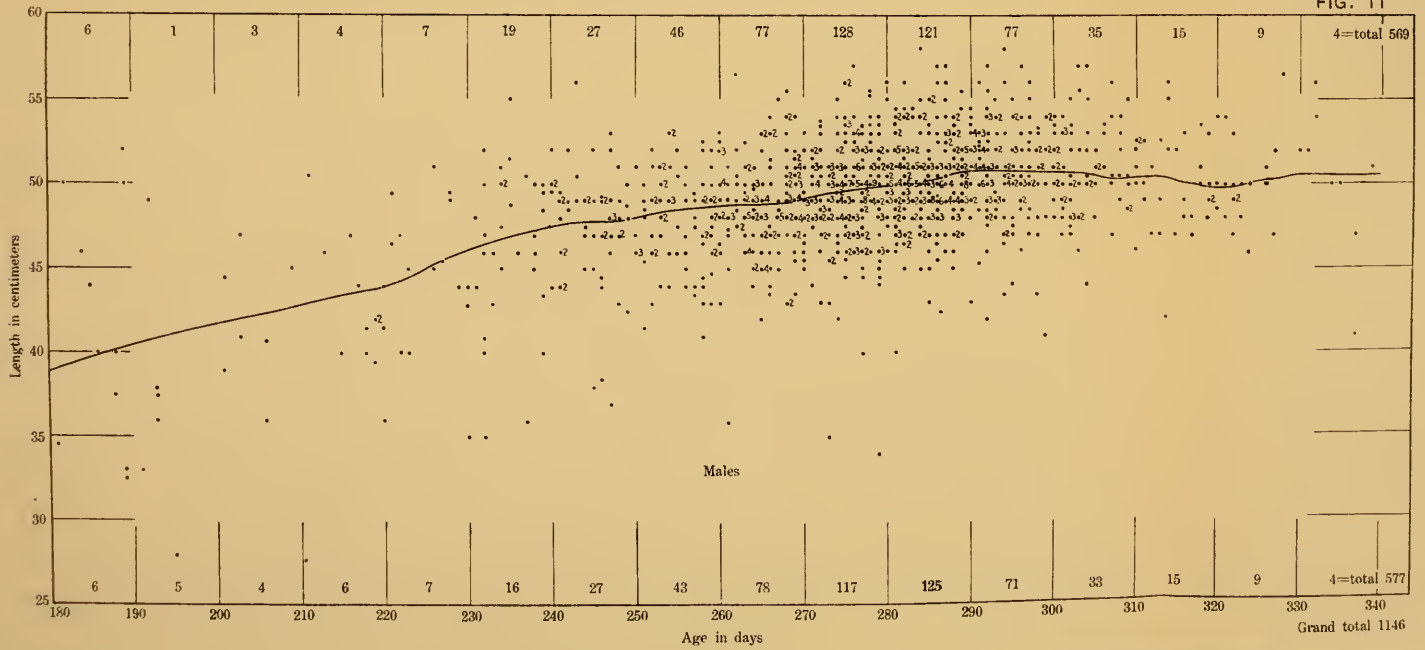

6 1 3 4 7 19 27 46 77 128 121 77 35 15 9 4=total 569
6 5 4 6 7 16 27 43 78 117 125 71 33 15 9 4=total 577
Length in centimeters
Males
Age in days
Grand total 1146

FIG. 12

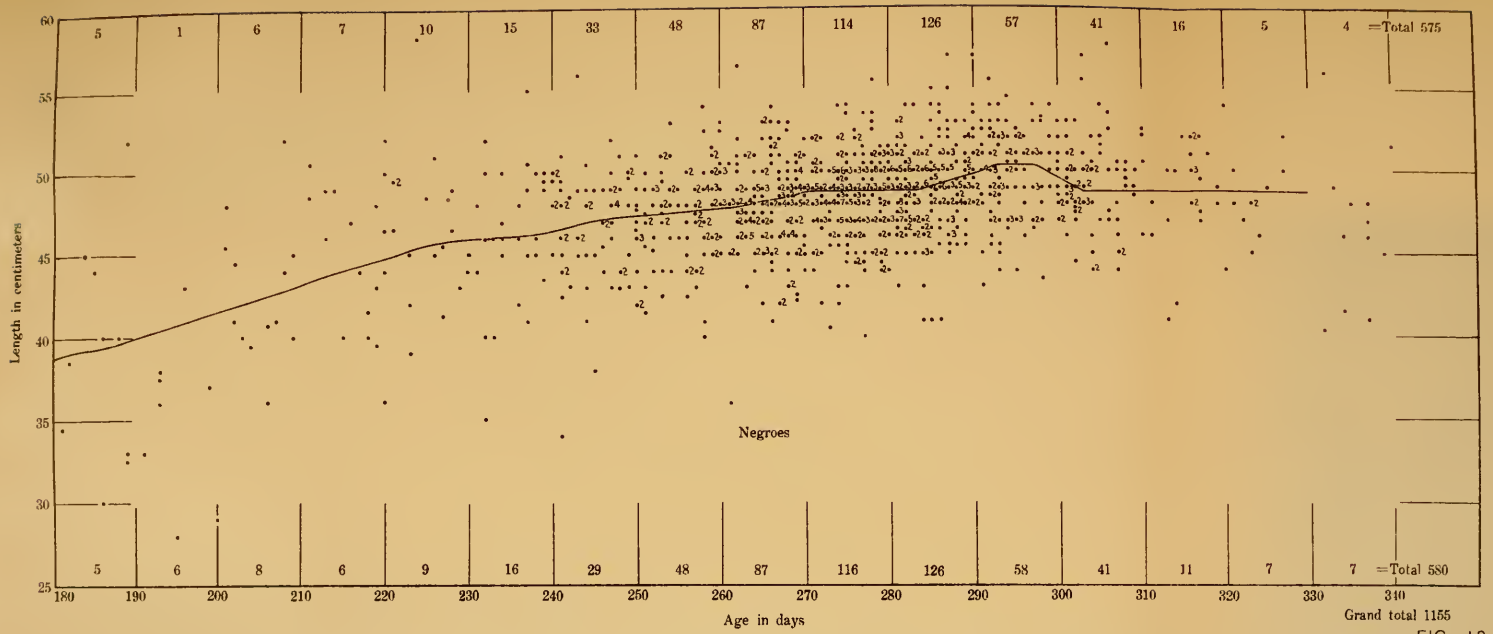
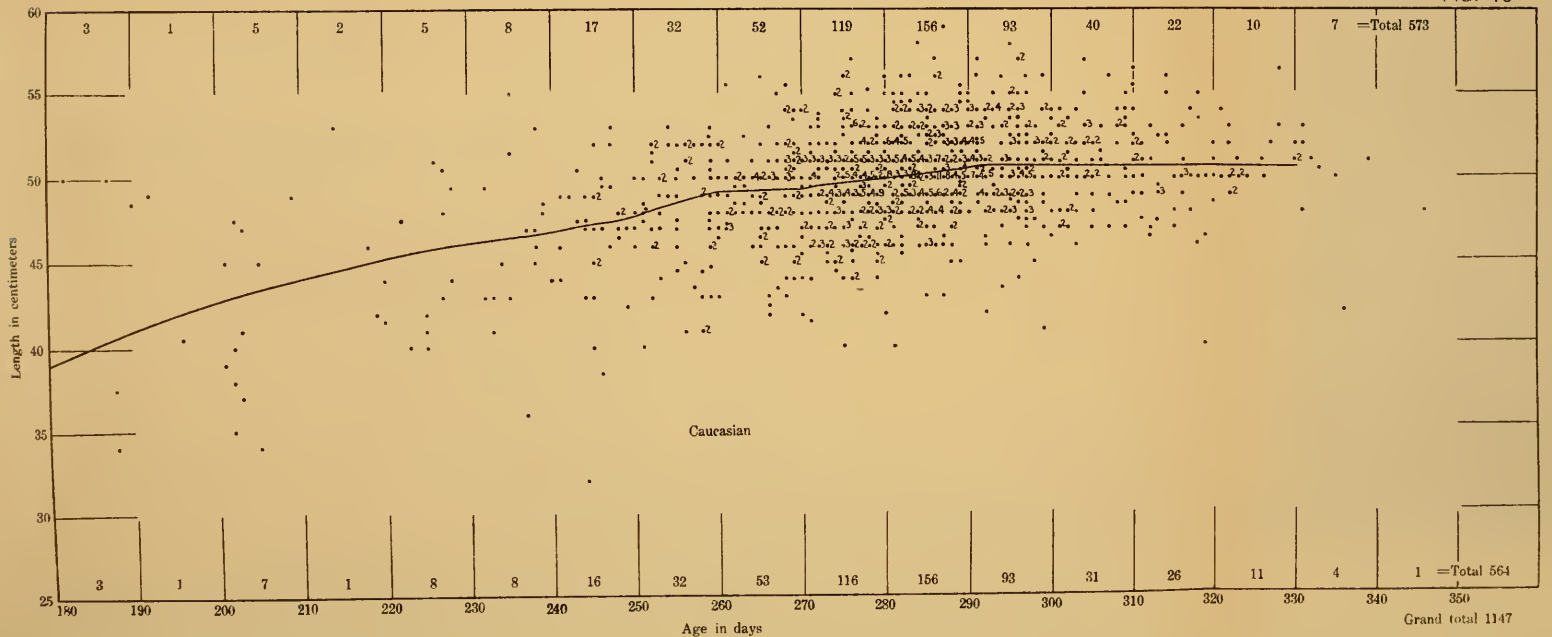

5 1 6 7 10 15 33 48 87 114 126 57 41 16 5 4 =Total 575
Length in centimeters
Negroes
5 6 8 6 9 16 29 48 87 116 126 58 41 11 7 7 =Total 580
Age in days
Grand total 1155

FIG. 13


3 1 5 2 5 8 17 32 52 119 156 93 40 22 10 7 =Total 573
Length in centimeters
Caucasian
3 1 7 1 8 8 16 32 53 116 156 93 31 26 11 4 1 =Total 564
Age in days
Grand total 1147

CONTRIBUTIONS TO EMBRYOLOGY, NO. 5.

THE CORPUS LUTEUM OF PREGNANCY, AS IT IS IN SWINE.

By George W. Corner.

With three plates.

CONTENTS.

	PAGE.
Introduction	71
Breeding habits of the sow	72
General features of the corpus luteum	72
Histology of the corpus luteum of the sow	73
Cytology of the lutein cell	75
Life history of the lutein cell of pregnancy	79
Previous observers on the corpus luteum at various stages of pregnancy	80
Characteristics of the corpus luteum at the various stages of pregnancy	81
Criteria of age of the corpus luteum	82
Theoretical considerations	84
Distinction between the corpus luteum of pregnancy and of ovulation	85
Influence of pregnancy on the structure and function of the Graafian follicles	86
Abnormalities of the lutein tissue	88
Migration of the ovum in the sow	90
Conclusions	92
Literature cited	93

THE CORPUS LUTEUM OF PREGNANCY, AS IT IS IN SWINE.

INTRODUCTION.

At the instance of Professor Mall, I have undertaken the studies to be presented in this paper, in the hope of gaining such knowledge as would enable us to draw up a standard description of the corpus luteum throughout its history. If we knew the exact appearance of the human corpus luteum at all its stages, especially during pregnancy, we should have an instrument of the greatest value in the solution of many complicated problems of embryology and physiology, and even of clinical gynecology and organotherapy. Since the path of such a research as I have here begun is as yet unblazed, and because studies of the human tissues are so hampered by pathological changes, faulty histories, and difficulties of collection and preservation, for the beginning we have limited ourselves to the ovary of the domestic sow, and have started out with the simple hope of obtaining an answer to one question: What is the appearance of the corpus luteum at each and every stage of pregnancy? To this query as simple an answer has been found, but the work has led in such unexpected directions and into such interesting by-ways that the reader will no doubt feel as much disappointment in reading as the author has in writing a paper which answers one question, only to raise a score as yet unsolved.

During the months of October 1913 to May 1914 I have collected from the hundreds of sows' uteri and adnexa obtained at the slaughter-house adjacent to this laboratory, 128 pairs of ovaries from pregnant animals, the embryos being in each case examined and measured. The youngest embryo studied had 5 somites, and its age was estimated at about 15 days. The specimen is preserved as pig embryo No. 10 in the embryological collection in this laboratory. The oldest fetus in my series was 290 mm. long, or just about at term. In this paper, where lengths are given, they represent careful crown-rump measurements. Since the age-length ratio of embryos of the pig has never been fully worked out, the ages given are only approximate, and were obtained, for the younger stages, by comparison with Keibel's lists and figures (1897), and for the older stages from a table found in Strangeways' "Veterinary Anatomy," and said to have been compiled from the works of Gurlt, Leyhs, Franck, and others. The entire uteri and adnexa were received at the laboratory within an hour after killing, generally within a few minutes, and while yet warm. The fixing agent used was 10 per cent aqueous solution of formalin (40 per cent formaldehyde). The preparations were made by cannulating the ovarian artery, or the uterine, in which latter case it was advisable to tie off a few branches. The blood-vessels of the ovary were then injected with the formalin solution heated to 40° to 50° centigrade, and were placed in the same fluid. In a few cases where injection was not possible or not successful, the corpora were sliced with a razor-blade and the ovaries immersed in the warm formalin. For the study of the fat-content of the tissue, slices were cut from certain of the fresh corpora lutea and fixed in 2 per cent osmic acid for 24 hours. In all cases the ovaries were numbered consecutively, the right and left ovaries being indicated, the embryo pigs were measured, and the number of them in each horn of the uterus recorded.

The specimens were left in the formalin 24 to 48 hours, the solution having been allowed to cool an hour or two after immersing the specimens. After fixing they were washed in running water 24 hours, then dehydrated by passing through graded alcohols for 24 hours each (30, 40, 50, 60, 65, 70, 75, 80 per cent). The whole ovaries were then placed in

80 per cent alcohol for preservation, and blocks cut from them for sectioning were put for 24 hours in each of the following fluids: 85, 90, 95, 98 per cent alcohol, equal parts 98 per cent alcohol and ether, celloidin solutions 2, 4, 6, 8, 10, 12, 14 per cent. Finally the celloidin blocks were hardened with chloroform. As a routine, from one corpus luteum of each ovary or pair of ovaries two sections were made, 10 or 15 microns in thickness (the sections often passed through two adjacent corpora lutea), and in addition sections were made of any unusual or puzzling structure. Of these two routine sections one was stained with eosin and Ehrlich's hematoxylin, the other with Mallory's triple connective-tissue stain (acid fuchsin, phosphomolybdic acid, aniline blue, and orange G). The latter staining method is particularly valuable, since it not only gives beautiful pictures of the connective tissue, but also of those very structures of the lutein cells which are most important for the present study.

BREEDING HABITS OF THE SOW.

The females of the wild swine are monestrous and give birth to one litter a year, according to Kaeppeli (1908). But in domestication the sow undergoes an estrous cycle lasting 2 to 4 weeks, generally 3 weeks (Kaeppeli, Fleming: Veterinary Obstetrics). If the animal becomes pregnant, she may conceive again 5 weeks after delivery. The period of gestation is 16 to 17 weeks, usually between 116 and 120 days. Farmers commonly arrange to have litters produced in the spring and autumn, but in the material received at this laboratory, from stock raised for slaughter, fetuses are found in all stages of development, without great regard to the time of year.

The domestic sow is a very prolific animal, sometimes giving birth to as many as 19 pigs in one litter. Wentworth (1914) mentions an extreme case in which a sow gave birth to 23 pigs in one litter. John Hunter kept a record of the total progeny of one sow, in order to have a control for another, one of whose ovaries he had removed. During her life the normal animal gave birth to 13 litters, numbering in all 162 pigs, making an average of 12.5 pigs for each birth. In animals sent to the city for slaughter such high figures do not occur, for several reasons. The animals are sold young, often while bearing their first litters, which are commonly small in number; or if they are multiparæ, they are sold for the very reason that they are not profilic breeders. Moreover, the stock sent to the slaughter-house is the general product of the country-side, not always from selected droves. My records show that 6 is the commonest number of pigs in one litter, the extremes being 1 and 10.

GENERAL FEATURES OF THE CORPUS LUTEUM.

On examining the ovary of the pregnant sow, the first objects to strike the eye are the extraordinarily prominent corpora lutea, which project nearly all their volume from the surface of the ovary. In each ovary of the domestic sow I have found from 1, or none, to 10 recent corpora lutea, and in both ovaries from 1 to 16, most commonly 8. For the reasons which I have given, these figures are lower than would be found in well-bred, selected stock. It will be noticed also that the pigs are commonly fewer than the corpora lutea; in other words, that frequently not all the ova expelled at one time develop into pigs. The corpora lutea are generally ovoid or spherical in form, with outside diameters of 8 to 10 mm., most often about $10\times10\times10$ mm. The full size is attained when the fetuses are about 10 mm. long, and does not change until retrogression of the corpus luteum is well advanced after delivery; in other animals the corpus luteum is said to increase slowly in size throughout pregnancy. (For instance, the bat, as studied by Van der Stricht, 1912.) The custom-

ary name, corpus luteum, does not apply to swine, for the color of the cut surface of the fresh organ is a light pinkish gray, which only changes to yellow in the old corpora.

Besides the 1 to 10 corpora lutea in a given ovary, which experience shows mark the site of the ovulation which led to the pregnancy, there are often a number of smaller corpora lutea, which are bright yellow in color, and on section prove to consist mainly of dense connective tissue. In some ovaries there is still another older generation, dating from the second previous ovulation, which are seen as small white bodies nearly buried in the ovary. The remains of corpora lutea older than the second previous generation are not usually visible on gross examination, except as minute opaque bodies tucked in between the follicles and appearing in sections as the familiar hyaline areas. Since the corpus luteum remains as a distinct structure through the two succeeding ovulations, it follows that during the sexually active period of life the ovary should never be free from corpora lutea. This was true of the specimens examined by Kaeppeli (1908), but in our material there are many which contain nothing but follicles and what are apparently corpora lutea several periods old. Either these are atretic follicles, resembling corpora lutea, the sexually active period not having begun, or else it is not uncommon for the sow to pass an œstrual period without ovulation.

If, then, the corpus luteum is still evident after two successive ovulations following its formation, it becomes important to the progress of our study to know whether there is any likelihood of confusing the corpora lutea of two different generations. When two or more generations are present, by microscopical study we always find such marked histological differences that there is no possibility of confusion, but on naked-eye examination it is not uncommon to find corpora lutea apparently intermediate, in size and color, between the two obviously different groups present. I have submitted all such cases, 8 in number, to microscopical study, which showed that in 3 cases corpora lutea markedly smaller than their mates presented the same histological appearances. A typical instance is given by a specimen in which there were two corpora lutea of pregnancy 8 to 9 mm. in diameter, and another of the same histological appearance only 4 mm. in diameter. In another case it was necessary to section every corpus luteum of both ovaries to find how many of them were recent. The moral is that critical points regarding the age of corpora lutea can not be decided without microscopical evidence.

Important also are the questions as to whether the corpora lutea of both ovaries, dating from the same ovulation, present the same histological appearance, and whether all the corpora of one ovary, dating from the same ovulation, are alike. To answer these questions, I have examined sections taken from corpora lutea of both ovaries of 19 sows, and a larger number taken from two or more corpora lutea of single ovaries, with the simple result that all the corpora lutea of the same pregnancy, in both ovaries are in cytological structure absolutely identical. Sometimes the central cavity of the follicle lingers longer than in its mates, or there is a minor difference in size or other gross characteristic, but in microscopic structure never.

HISTOLOGY OF THE CORPUS LUTEUM OF THE SOW.

It is necessary, for the sake of clearness, to discuss briefly the perennial question of the ovary—that of the origin of the lutein cells—which above almost all other anatomical questions is notable for radical differences of opinion among the many capable investigators who have attacked it. The reader will recall that there are three views as to the source of the lutein cells of the mammalian corpus luteum. The first suggestion was that of von

Baer (1827), who believed that the lutein cells are derived from the connective tissue about the follicle, the theca interna; and the second is that of Bischoff (1842), who concluded that the cells come from the epithelial layer of the follicle, the membrana granulosa. The chief arguments in favor of the first view are that, firstly, as the Graafian follicle ripens, the theca cells show marked changes; they swell in volume, become rounded, and in short come to resemble the lutein cell very closely (see below, p. 86, and figures 16 and 18); secondly, the membrana granulosa of large follicles is often degenerated, and is believed to be cast off at the time of rupture; thirdly, such follicles as do not rupture are filled up by proliferation of the theca interna, and in this process of atresia become very much like corpora lutea. It is interesting to note that the latter view happens to have for prominent defenders those who have worked most carefully upon the sow's ovary, Benckiser (1884), Jankowski (1904), and Clark (1898). Great doubt has been cast upon it, however, by the careful and patient work of Sobotta (1896 ff.) and his followers, who maintain the origin of the lutein cells from the granulosa alone, and do not admit the participation of theca cells except to form the connective tissue reticulum.

A third theory, due I believe to Schrön (1863), but upheld recently by Rabl (1898), Seitz (1896), Leo Loeb (1906), R. Meyer (1911), Van der Stricht (1912), and others, is that both layers of the follicle form lutein cells. The upholders of this view do not deny one of the arguments of their opponents, that regarding the changes of the theca interna during the ripening process, but they think it is not permissible to draw conclusions from the resemblances between follicular atresia and corpus luteum formation. Moreover, it is not true that the granulosa is cast off from normal follicles before or at the time of rupture, as is well shown in figure 1. Many of those who believe that the theca cells take part in lutein-cell formation describe some of the "theca lutein cells," as they call them, remaining for a time in little groups about the periphery of the corpus luteum and along the septa of connective tissue which penetrate it.

I think it may be said with fairness that most of those who have really devoted themselves to accurate studies of the corpus luteum with modern methods maintain the origin of the lutein cells either from the granulosa or from both layers of the follicle. With only a few specimens of very early corpora lutea at hand, I can not presume to enter this controversy, except to mention that in the sow the granulosa undoubtedly persists after rupture of the follicle, and becomes vascularized by vessels from the theca interna. After this there is a gap in my series until the corpus luteum becomes solid. However, from some new points in the histology of the corpus luteum, which I am about to mention, it seems that in the sow, at least, there is a fourth possibility to be reckoned with by the investigator who is to clear up this baffling question—namely, that the granulosa and perhaps part of the theca enter into the formation of true lutein cells, while some of the cells of the theca interna remain as distinct cells of special nature in the fully formed corpora lutea.

It is apparent at first glance at a well-prepared section of the corpus luteum of the sow that it is not the simple structure composed of a parenchyma of lutein cells and a framework of connective tissue which is figured in the manuals of histology. The lutein cells are indeed the chief element, but lying between them are other cells of at least two sorts, which can be found at all stages of pregnancy. For want of better terms I shall denote them as additional cells of the corpus luteum, types 1 and 2.

Type 1 (fig. 2, *b*).—About the periphery of the corpus luteum, and along the septa of connective tissue which penetrate it, in many sections one sees small groups of cells which have the following characteristics: round or oval nuclei containing a moderate amount of

chromatin (more than the true lutein cells), and smoothly staining, very finely granular cytoplasm. The cells are round, or slightly elongated in one direction, and are smaller than the lutein cells, having a diameter of 15 to 20 microns. Now, if we examine the figures of some upholders of the compromise or joint-origin theory of the corpus luteum, for instance, those of R. Meyer (1911), we find that they show cells of this same appearance in this same situation, which are described in the text as cells of the theca interna, not yet changed into lutein cells or connective-tissue cells. Are these cells which I have described in the pig identical with the so-called theca lutein cells? The evidence for this view lies in the facts that they are present in the early stages of pregnancy, are then very distinct from the ordinary lutein cells, and lie mostly in the position in which the theca lutein cells are described. Against it is the fact that when the corpus luteum undergoes certain changes to be described later as distinctive of the latter part of pregnancy, these cells seem to increase in number, they follow the growing connective-tissue reticulum into all parts of the corpus luteum, and they come to resemble the true lutein cells very closely; indeed, at times it is almost impossible to distinguish them; whence it might be inferred that the two sorts of cells are different only in state of activity. The origin of these cells must be left without further definite statement, although we shall come back to them later, as they form part of our criteria for determining the age of the corpus luteum by microscopical examination.

Type 2 (fig. 3, *b*).—These are cells of varying form and size, generally rather smaller than the lutein cells, ranging in shape from spindles to branching and spherical forms, having a cytoplasm which stains deeply with eosin, and takes a dark brown or purple color with Mallory's stain, but sometimes takes instead the aniline blue ingredient of the mixture. Very often the cytoplasm is filled with minute vacuoles which appear as bright, highly refractile granules about 1 to 2 microns in diameter. No matter what fixing reagent and stain is used, they remain vacuoles, and may even be found in osmic-acid material. The same vacuoles may occasionally be found in the lutein cells. I have not seen these cells in fresh teased preparations. They are not numerous; in one section from a very few to a hundred may be seen scattered among the hundreds of lutein cells, but they are not found in all ovaries, although they are easily seen, because of their dark stain and the fact that their cytoplasm is usually slightly shrunken, and hence they stand out distinctly. They seem to have been observed previously only by Delestre, who saw them, if I interpret his description aright, in the corpora lutea of cows (1910). As to the nature of these cells, it is difficult to say whether they represent a modification of the lutein cells or of the connective tissue. There seem to be transitions in both directions. But there is perhaps a clue in the specimen illustrated in figure 1, of a very recently ruptured follicle, in which the layer of theca interna cells nearest the granulosa is partly composed of cells similar in size, shape, appearance, and staining reactions to the cells in question. The significance of the cells is totally obscure to me.

CYTOLOGY OF THE LUTEIN CELL.

The lutein cell possesses the elementary structures found in all animal cells. The nucleus, which in the active stages of the corpus luteum is round, vesicular, and poor in chromatin, has one or more large nucleoli. The cytoplasm, at certain stages to be specified below, is differentiated into two portions: an inner dense zone, the endoplasm, which in fixed specimens appears to be very finely granular, and an outer zone, the exoplasm. This latter zone, whether studied in fresh preparations or in carefully fixed sections, is of the most astonishing complexity. It is so full of granules and globules of diverse substances

that the nucleus of the fresh cell can sometimes hardly be seen. Some of these granules are mitochondria; this may very easily be confirmed by making a preparation of fresh teased cells with Janus green; this dye gives a vital stain of the mitochondria, as shown by Bensley (1911). Other globules are fatty and are selectively stained, for the purpose of analyzing the cell elements, by any of the usual methods for neutral fats, such as Sudan III and osmic acid. The nature of the fatty substance of the lutein cell, as found in the horse, cow, and sow, has been studied microchemically by Cesa-Bianchi (1908), who thinks it is lecithin; the existence of this substance in the corpora lutea had previously been declared by Loisel (1904) on the basis of test-tube analyses. A striking contrast to the statements just made is offered by the report of J. W. Miller (1910) upon his studies of the human ovary, in which he states emphatically that there is no substance in the fresh corpus luteum of pregnancy which gives the reactions of the neutral fats, and that such reactions are obtained only during the puerperium; that is to say, in retrogressive corpora lutea. On the other hand, the lutein cell of the cat is often so honeycombed with fat that the vacuoles resulting from the action of alcohol and ether obscure the finer structure of the cell, so that I found it impossible to use some cats' ovaries which were at hand, in studies to corroborate the results of this research.

The most comprehensive description of the fatty inclusions in the lutein cells is that of Van der Stricht (1912), who worked with the ovaries of several species of bats. He finds the cells of young corpora lutea loaded with osmic-blackening material, but that there is a gradual decrease in amount of this substance until the latter part of pregnancy, when globules again begin to be deposited. It is his opinion that the early deposit of fat is epithelial in nature, representing a secretion of the corpus luteum, but that the later reappearance of presumably fatty material is a sign of senescence of the tissue. I shall detail my findings in the sows' lutein cells later; it suffices to say here that my preparations agree fully with those of Van der Stricht, in spite of the great difference in zoological position of the animals used.

In celloidin sections of corpora lutea from animals containing fetuses less than 40 mm. long, fixed with such common solutions as formalin, absolute alcohol, and bichloride of mercury, in which neither the fat nor mitochondria are preserved; and in osmic acid preparations, in which the fat is distinguished by its intensely black color, we find the peripheral part of every cell, the exoplasm, occupied by a most curious maze of clear spaces, of protean form, alternating with rings and rod-shaped masses of cytoplasmic material, which give the cell an almost indescribable but striking appearance (fig. 4).

Since these peculiar structures are found to be important guides in following the history of the lutein cell, it will be advisable to review briefly the conclusions of other investigators regarding similar appearances in other cells. In 1898 Golgi reported that in preparations of nerve cells from the central nervous system, made by a method of chrome-silver impregnation, he found the metallic substance deposited in the form of a network which lay in the cytoplasmic portion of the cell. This structure he called the "Apparato reticulare interno." About the same time Nelis and Holmgren both described net-like or strand-like appearances in the cytoplasm of nerve cells, which were seen as unstained areas in sections colored by dyes. Nelis called these structures "état spirémateux du protoplasm" and Holmgren applied the term "Saftkanälchen" and later "trophospongium" to the essentially similar structures which he had found.

As these canals began to be discovered in nerve cells of all kinds, and then in cells of many other organs, their importance was recognized, and the many questions connected

with them were vigorously discussed. Golgi denied the identity of his reticular apparatus with the trophospongium, but Holmgren affirmed it, at least in part. The latter view has taken the ascendant. Ramón y Cajal believes them to be identical (1908). Cowdry (1912), from the study of specimens prepared by the methods advocated by both discoverers, points out the great similarity of the two phenomena.

The functional importance assigned to the reticular apparatus by different authors is varied. It seems well established that the appearances are not artifacts, but are present during life. Some have thought them excretory channels, others circulatory paths for cell juices. Holmgren thinks they are often entered by processes of the connective-tissue cells and that they are the morphological expression of vital processes such as the formation of secretion droplets and the like. According to this view the system of canaliculi is an unstable, constantly changing structure, like any other physiologically active organ, a view which explains the variability of the histological appearance. Most investigators have conceived the reticular apparatus to be a constant component of the cells in which it is found, but von Bergen (1904), who studied the canaliculi in a great variety of cells from many organs, maintains the transitory nature of the structure. This latter opinion is certainly borne out by the study of the lutein cells, as will be shown later.

Cohn (1903), in a careful paper on the histology of the corpus luteum, states that he was unable to see the trophospongium in the lutein cell, although he had followed the methods of Holmgren; but Vastarini-Cresi (1904), in a short note, mentions, without describing, certain preparations which he had demonstrated at Naples in 1904. Cesa-Bianchi (1908) describes and figures lutein cells of swine which show appearances resembling the trophospongium as observed in other cells. By the Golgi method Riquier (1910) demonstrated an intracellular reticular apparatus in the lutein cells of the cow and, what is very important in connection with the findings to be described in this paper, he showed that the structures undergo marked changes with the advancing age of the cell.

Now, if we take a well-prepared section of the corpus luteum of a pregnant sow, whose fetuses are perhaps 100 mm. long, and stain it with any strong cytoplasmic stain (Mallory's does excellently), careful study of the lutein cells shows that the cytoplasm contains unstained areas which are roughly concentric to the nucleus, and which appear to form canal-like paths in the cell (fig. 8). If we take younger corpora lutea, we find the canalicular apparatus growing more and more complex. It assumes the form of wide V-shaped spaces, long clefts, and circles in the cytoplasm, so extensive that the nucleus is surrounded by only a narrow zone of endoplasm (fig. 7). But it is in the corpora lutea of pregnancies under 30 mm. that the highest development of the exoplasm is found (figs. 4 and 5). Here the exoplasm is occupied by a most curious and elaborate system of vacuoles, almost every one of which in turn contains a spherule of substance which, although it takes the same stain as the cytoplasm, yet has a more hyaline appearance, and is seen on section as a bright ring. Within many of the spherules is found another and tiny vacuole.

Curiously enough, the only investigator who has previously described this remarkable state of the lutein cells is F. Cohn (1903), who is mentioned above as denying the existence of the trophospongium in lutein cells. He observed all the appearances which have just been mentioned, in the corpus luteum of the rabbit at the height of its development, and undertook certain microchemical studies on their nature. He found that the innermost tiny vacuole contains a substance which blackens with osmic acid, presumably fat. In the sow's corpus luteum (fig. 6, *a*) I have been able to confirm this observation of Cohn, but not his other observation, namely, that the outermost vacuole, or clear space about the

hyaline ring, is stainable with one of the methods for demonstrating myelin, Plessen and Rabinowitz's modification of Weigert's hematoxylin. I have seen the ring-like structures in tissue fixed with formalin, osmic acid, saturated mercuric chloride, Zenker's fluid, and absolute alcohol. Although I have not made an extensive search for these formations in various species, I have looked through a number of specimens prepared for other purposes which chanced to be at hand in the laboratory, and found the ring-like bodies in corpora lutea of the human species, the dog, and the cat. Add to these Cohn's original description in the rabbit, and we have seen the peculiar exoplasmic rings in the corpora lutea of ungulates, carnivora, rodents, and primates—surely a general distribution among the higher mammalia. Van der Stricht, in his long paper on secretory appearances in the corpora lutea of bats (1912), does not mention them, but the lutein cells of the bat (as are often those of the cat) are heavily loaded with fatty matter which would obscure the other details of the cytoplasm.

To avoid making an unproved assumption, in this paper I shall refer to these formations merely as exoplasmic formations, but I think there can be very little doubt that they are really one stage of the canalicular apparatus of Golgi-Holmgren, although granules within the canaliculi have never been described in other cells. In the first place, they can be traced back directly through all transitions from cells containing the classical form of trophospongium (figs. 4 to 10). In the second place, ring-like canaliculi are not new. Cattaneo (1914), in a paper on the canalicular apparatus of ovarian ova, figures appearances not unlike those under discussion, except that he shows no bodies within the canaliculi; and Bensley (1910) has shown very similar spaces in the root-tip cells of the onion. The ring-like structures are so beautiful and so striking that one wonders why they have not been emphasized long ago by some of those who have studied the ovary. Still, they require the best of fixation, and in the usual eosin stain are not as visible, as with Mallory's connective-tissue stain and others which give a strong coloring of the cytoplasm. Yet I think they have been seen before and misunderstood. For instance, J. G. Clark (1898) states that the lutein cells of swine become full of vacuoles and their cytoplasm becomes shrunken, but he was probably actually describing the exoplasmic vacuoles, which we shall see to be evidences of cellular activity, not of senescence.

There is still another important histological element of the lutein cell to be considered, namely, certain granules of the endoplasmic zone which were described by Cesa-Bianchi in 1908. He found, in the perinuclear portions of the cell, a large number of densely packed granules about 1 micron in diameter. To demonstrate them, since the multitude of cytoplasmic structures makes them difficult to see in the living cell, he fixes the tissue in Zenker's fluid or saturated mercuric chloride, sections it in paraffin, and stains with any one of a number of staining combinations, especially hemalum-safranin light green, iron hematoxylin, and Mann's complicated methyl-blue-eosin stain. I have repeated the Zenker safranin light green method, but I find that the granules show up fairly well in formalin tissue stained with hematoxylin and eosin, and very well with Mallory's triple connective-tissue stain; indeed, I had observed them in my preparations before I knew of Cesa-Bianchi's work. In tissue fixed with osmic acid they appear as dark-gray granules against the light-gray endoplasm (fig. 9, *c*). With Mallory's stain they generally take the orange constituent of the mixture and appear as bright round bodies against a blue-gray background (fig. 7, *c*); but when the sections take the aniline blue ingredient of the stain more strongly—as they sometimes do, with the result that the nucleus becomes blue—it is interesting to note that the endoplasmic granules also stain blue. Cesa-Bianchi's figures,

which are rather diagrammatic, show the granules clustered closely about the nucleus, but I generally find them more or less diffusely scattered through the endoplasm. When the endoplasm reaches to the periphery, as it does in the later stages, then consequently the granules are seen throughout the cell. As to their nature and function we can only guess. As they are not dissolved from fixed tissues by ether, alcohol, or water, and because they are preserved by mercury salts, Cesa-Bianchi thinks they are of albuminous nature. I see no reason to think otherwise, although one hesitates to speculate on the chemical nature during life of minute objects which one does not see until they have been through 50 to 70 changes of reagents. It has impressed me strongly that the staining reactions of the endoplasmic granules are the same as those of the peculiar rings found in the exoplasm. Now, in the life-history of the lutein cell, as we shall see later, the exoplasm recedes as the endoplasm becomes wider, and the granules seem to increase in proportion to the amount of the endoplasm. It occurs to me that possibly the two structures are but stages in the same process. Cesa-Bianchi presumes the granules to be connected with the supposed phenomena of internal secretion of the corpus luteum, and that his findings support the theory of an internal secretion; a view based of course on analogy, but one which must be kept in mind.

In the corpus luteum of the sow I do not observe the yellow granules of pigment which are said to be plainly visible in the corpus of the cow, and concerning which the remarkable discovery has recently been made by Escher (1913) that in chemical composition the substance is identical in all reactions with the lipochrome body carotin, found in carrots and green leaves.

LIFE HISTORY OF THE LUTEIN CELL OF PREGNANCY.

In the earliest corpus luteum of known age of pregnancy in my series of sections, the lutein cells are fully formed and contain the peripheral ring-apparatus in a high state of development. In discussing them at an earlier stage we tread upon debatable ground. In a specimen to be described at length (p. 88, figs. 21, 22, 23), as an illustration of the interesting anomaly known as partial accessory lutein-cell formation, the cells of the granulosa of the follicle in question, at the point where the supposed lutein-cell formation is taking place, are swollen, possess vesicular nuclei, and contain in their cytoplasm very definite canals having within them a few minute hyaline rings. The resemblance to the fully formed lutein cell is striking.

In corpora lutea of pregnancy of 20 to 25 mm., all the lutein cells are of about the same size, are rounded in outline, and possess round vesicular nuclei relatively rich in chromatin. The endoplasmic zone is almost nil, being crowded out by the great development of the exoplasmic formations. The latter are composed of the ring-like structures previously described, in a high stage of perfection. At this time the cells contain considerable quantities of osmic-blackening substance, which almost fills some of the cells with good-sized globules of varying magnitude, besides occurring, as shown by Cohn, in tiny droplets at the centers of the spherical structures of the peripheral vacuolar apparatus (fig. 6, *a*).

As the cells grow older the following changes take place, as shown in figures 4 to 15:

(1) The nuclei become paler by reason of the lessening of the chromatin.

(2) The ring-like formations give place to less elaborate forms; that is, to simple clefts and V-shaped spaces in the cytoplasm, arranged concentrically to the nucleus. In corpora lutea of old pregnancies (150 to 290 mm.) no sign of the once elaborate structure is to be found in most cells.

(3) The fat content changes, at first decreasing. In the cells of the type most abundant at the middle of pregnancy, in which the endoplasmic zone occupies half or more of the cytoplasmic area, the globules of osmic-blackening material are found in amount much less than at previous stages, and clustered at the margin between exoplasm and endoplasm. Toward the end of pregnancy, when the fetuses are 200 mm. or more in length, the lipoid material has practically disappeared from the cell, being found, if present, as a few globules at the periphery. But still later, in the corpora lutea of pregnancies of 270 mm. or longer, many cells contain one or two globules twice as large as those previously seen, and which are often observed in ordinary sections as large vacuoles, sometimes as large as the nucleus, in the cytoplasm. This later deposition of fat I take to be a sign of senility of the tissue, whereas the large amount of lipoid in the early lutein cell would seem to be correlated with physiological activity. I have already mentioned the similar conclusion of Van der Stricht regarding the corpora lutea of the bat. It is very interesting to note that the occurrence of fatty substances in the connective-tissue cells and in those cells which I have called type 1 is in inverse ratio to that of the lutein cells. At 20 mm. only relatively few and very small osmic-blackening granules are found in the spindle cells, but as pregnancy advances fat is deposited in larger and larger masses until at 250 mm. the nuclei of nearly all the interstitial connective-tissue cells are hidden by the large, closely packed fat globules.

(4) Another change with advancing age of the fetuses is in the chromatic granules of the endoplasm, which appear to grow larger and more apparent, reaching sometimes a diameter of 2 microns.

Throughout all this change the size of the lutein cell remains practically the same.

PREVIOUS OBSERVERS ON THE CORPUS LUTEUM AT VARIOUS STAGES OF PREGNANCY.

While it has been recognized in a vague way by some authors that the corpus luteum is not the same at all stages of pregnancy, others hold that after the organ is formed it maintains its structure in the same state until delivery or at least until retrogression sets in, as, for instance, Ravano (1907) and R. Meyer (1911). At any rate, the attempt has never been made to trace the changes carefully and to relate the corpus to the stage of the fetus at all times of pregnancy. In general, investigators have recognized merely three stages of the corpus luteum, namely *formation*, *maturity*, and *retrogression*. Robert Meyer would divide the first stage into two, *proliferation* and *vascularization*. Cesa-Bianchi, on the basis of his work on the evidences of internal secretion in the corpus luteum of swine, mares, and cows, mentioned above (1908), finds three stages of the lutein cells. In the first or preparatory period, the lutein cells are of relatively small dimensions (15 to 20 microns), with clear and regular contour, round or oval form, nucleus almost central, with rich chromatic net and marked nucleolus, protoplasm homogeneous or uniformly granular, not presenting granules, vacuoles, or inclusions. This description does not fit the stage of formation as I find it in the sow, but it is not easy to say at what time of pregnancy Cesa-Bianchi places his first stage, as he does not give full measurements. His second period is characterized by the presence of abundant granulations in the cytoplasm. The lutein cells are 30 to 40 microns in diameter; in form they are irregularly polyhedral, with excentric nuclei which are vesicular, poor in chromatin, and possess numerous nucleoli. The cytoplasm presents two zones: the endoplasm, directly encircling the nucleus and filled with the chromatic granules described by him; and the exoplasm, presenting vacuoles of varying size. The third period is characterized by the presence in the cytoplasm of numerous drops of fat.

In 1910 Delestre published, from the Clinique Baudeloque, the results of his studies in this direction, using the cow as the subject of his work, on account of the fact that the term of pregnancy is very nearly that of the human, being 284 to 285 days. Unfortunately his youngest corpus luteum of pregnancy dated from about $2\frac{1}{2}$ months, the snout-rump length of the calf being 12 cm., so that he missed the very stage at which the exoplasmic apparatus is at its height, if the sow's corpora lutea are like the cow's. At this stage he describes four cellular elements of the corpus luteum: (1) The lutein cells, presenting no particular feature. (2) Cells somewhat larger than the lutein cells, having lightly staining protoplasm. I do not know what these may be, as I have not seen them in the sow. (3) Plasmodial masses with 5 or 6 nuclei, destined to form young lutein cells. I have not seen these in the sow. (4) Cells which, if I interpret the description rightly, are like those mentioned above as additional cells of the corpus luteum, type 2. Delestre states that at 4 months the plasmodial masses have disappeared, giving rise to young lutein cells, which are smaller than adult lutein cells, and are grouped, several together, in one mesh of the connective tissue. There are now two sorts of lutein cells, one containing fat, the other free of fat. At $4\frac{1}{2}$ months the number of cells containing fat is augmented and the young cells are rare. At 5 months all the young cells have disappeared and the adult features predominate, most of the cells containing fat. At this time signs of degeneration appear, in the form of vagueness of outline of some of the cells, poor staining reaction, and dried-up skeleton-like nucleus.

Delestre gives a comparative table of the characteristics of the corpus luteum at the beginning and end of pregnancy, which in most particulars applies equally well to the sow, although I can not confirm his account of the formation of young lutein cells from plasmodial masses, nor the description of degenerating cells at such an early time. With these simple outlines of the life-history of the corpus luteum as described by previous investigators, and with the extensive cytological data now at hand, we have the tools for the main part of our task, which is to relate the changing anatomy of the corpus luteum to the stages of advancing pregnancy.

CHARACTERISTICS OF THE CORPUS LUTEUM AT THE VARIOUS STAGES OF PREGNANCY.

I had hoped that the gross characteristics of the corpus luteum would be of help in the problem at hand, but I have been forced to the conclusion that the differentiation of corpora lutea of varying ages is only to be made with the oil-immersion lens. The corpus luteum of the youngest pregnancy in my series is already solid, so we gain nothing from the size of the central cavity, as we might in other species, such as the human, in which the cavity lingers longer. The blood-vascular system changes little during pregnancy, since there is the same amount of tissue to be supplied. The color is variable and gives no distinction of age. Sometimes in early corpora lutea the rapid increase in volume of lutein tissue causes a bulging of the inner substance of the corpus luteum through the point of rupture, the so-called "Propf" of the German writers. If we find an ovary in which the corpora lutea possess "Propfen," or several of the corpora contain slight remains of the former central cavity in the form of small spaces containing old blood, then probably the ovulation was fairly recent; but, on the other hand, in pregnancies of the first month the corpora lutea are often solid and homogeneous.

We must resort, then, to the immersion lens and a study of finer histological details. Because it will make the results more convincing, I shall mention briefly the method by

which the material was studied. As stated in the introduction, all the specimens had been prepared in the same way. All the specimens from pregnancies of 20 to 25 mm. were taken together and carefully studied, then all those from pregnancies of 50 to 55 mm., and so forth; and in this way was obtained an idea of the nature of the corpus luteum at a series of stages from an early period to term. Next the specimens of intervening length were examined, and finally from these observations it was found possible to divide the life of the corpus luteum into a number of definite periods according to the length of the fetus. When I was sure of being on firm ground, I began to go through box after box of sections, registering a diagnosis of the age of each corpus luteum, and then looking it up in the records. With increasing experience it became possible to place the specimen in its proper period practically every time, never varying from the correct stage by more than one of the seven periods of pregnancy. Of course these periods into which I have found it possible to rank my specimens are purely empirical, and represent lines which I have drawn at the limits of my ability to distinguish the stages of the cytological changes. I had at first several more periods interpolated between those given, but found that I could not regularly distinguish them. In short, it can generally be told, by examination of a section of a corpus luteum, on the basis of distinguishing characteristics to be given below, in which one of the following periods of pregnancy the specimen falls:

	Period.	Length of pigs, in millimeters.
1	Preparatory period	Less than 20
2	Exoplasmic development, first part	20 to 30
3	Exoplasmic development, second part	30 to 55
4	Transition period	55 to 140
5	Endoplasmic development, first part	140 to 170
6	Endoplasmic development, second part	170 to 220
7	Beginning retrogression	220 to 290

Needless to say, the corpus luteum, being an organic body, presents considerable variety of structure, so that these periods overlap, and pass gradually into each other, in such a way that, besides the specimens which fall near a border-line and hence are naturally difficult to place, a small number give an appearance which experience shows is normal to corpora lutea of older or younger age, just as in a series of embryos a few will exceed or fall behind the others in development.

CRITERIA OF AGE OF THE CORPUS LUTEUM.

First period: preparation.—Pigs less than 20 mm. long, duration of pregnancy less than 25 days (fig. 4). The corpus luteum of pregnancy does not attain full size until the twentieth day or thereabouts, but variation in size is so marked that no dependence is to be placed on dimension as a sign of early corpora lutea. On section the following features may be noted: The tissue is very densely packed, so that the nuclei of the slender connective-tissue cells seem relatively numerous. The septa of connective-tissue fibers are rather marked, but are narrow and compressed, and still preserve the radial arrangement in which they invaded the space. Between them are packed the lutein cells, which are polymorphic, but usually elongated in the direction of the radius of the corpus luteum; they are much more varied in size than in the succeeding stages. The nuclei are more chromatic than they will be found later. The ring-forms occur in every lutein cell, and are so large and

numerous that there is practically no endoplasm. Fat is present in great quantity in the lutein cells, as in the next stage, under which it will be described. In the interstitial connective-tissue cells of the corpus luteum there is a moderate quantity of fat in fine granules.

Second period: height of exoplasmic development.—Pigs 20 to 30 mm. long, approximate duration of pregnancy 25 to 30 days (fig. 5). The striking feature of this stage is that all the lutein cells are in the same state. All tend to be rounded in outline, all are of the same size, and show a uniform development of the exoplasmic apparatus, with ring-forms in every cell. The endoplasm is still very limited in amount. The nucleus is not so chromatic as in the previous period. Osmic-blackening substance is present in considerable amount in the lutein cells, in some cases almost filling the cells with globules of diameters varying from 2 to 5 microns. In the most typical cases the globules are thickly clumped at one end of the cell, or at both, but there is often a cluster of fat globules about the nucleus; indeed, at this stage the distribution of fat is almost general, at least in the lutein cells. However, the connective-tissue cells show little fat; in osmic preparations they show at most a few small black granules (fig. 6).

Third period: height of exoplasmic development, second part.—Pigs 30 to 55 mm. long, approximate duration of pregnancy 30 to 40 days (fig. 7). The previous stage passes insensibly into this, in which in many cells the exoplasmic structure is more varied in form; some cells contain the ring-forms (fig. 7, *a*), others present irregular channels and clefts (fig. 7, *b*). The endoplasmic zone about the nucleus can now be seen, and in a very few cells reaches to the periphery, in which case there are no peripheral spaces in the cytoplasm. In the endoplasm are seen the chromatic granules described by Cesa-Bianchi (fig. 7, *c*).

Fourth period: transition.—Pigs 55 to 140 mm. long, approximate duration of pregnancy 40 to 75 days (fig. 8). The ring-structures are disappearing, and become rare in the latter half of this stage. I have seen them but once or twice in ovaries from pregnancies above 140 mm., and therefore set that as the upper limit of the period. It is noted that the progressive changes of the cells are a little earlier at the periphery of the corpus luteum than at the center, and hence estimates of the age of the corpus luteum must be based upon a study of the whole area, giving more weight to the state of the peripheral tissue. In the earlier half of this period one sees an occasional cell without any exoplasmic clear areas or channels; in other words the entire cell, from nucleus to border, is occupied by the homogeneous endoplasm. Such cells become fairly common toward the latter half of the period, and in some fields of the lens may form half of the lutein cells. Fat has decreased in quantity in the lutein cells, where it is found chiefly at the border between endoplasm and exoplasm. In the lutein cells it occurs in globules of varying size (fig. 9, *a*), but in the connective-tissue cells in smaller granules only (fig. 9, *b*).

Fifth period: endoplasmic development.—Pigs 140 to 170 mm. long, approximate duration of pregnancy 75 to 105 days (fig. 10). A marked change has taken place in the corpus luteum, although it is not strikingly shown in the figure—a change which has for its most obvious feature a great increase in the diversity of the cells. Although the ring-forms have disappeared from all but a rare cell or two, yet many cells show considerable peripheral canalization. Next to such a cell may be a lutein cell which shows only endoplasm (fig. 10, *a*). Moreover, there has been an increase in the amount of connective tissue, so that in many sections the lutein cells are somewhat spread apart. Between them, adding to the diversity of appearance, lie the several kinds of cells which we have mentioned as members of this complicated structure, namely, the branching or spindle cells of the connective tissue, with their product, the reticular fibrils; the darkly staining cells which

I have called type 2; and, most notable of all, many cells of that type which I have called additional cells of the corpus luteum, type 1, which, with their nuclei, more chromatic than that of the lutein cell, and their homogeneous cytoplasm, resemble the "theca lutein cells" of other writers (fig. 10, *b*). With the increase of the connective tissue, penetrating between and spacing apart the true lutein cells, these smaller, homogeneous cells are found much more generally scattered through the corpus luteum than before. In osmic preparations they are often loaded with large densely-packed black granules (fig. 11, *a*). Others of the interstitial cells of the corpus luteum, of all types, contain only fine, diffusely scattered black granules (fig. 11, *b*). In the lutein cells themselves the amount of osmic-staining matter is progressively lessening; the globules are found in a narrow zone at or near the periphery of the cell. I think that most of the vacuoles seen at the border of the cell in Mallory's material at this stage are due to the fatty substance, and that the lesser number only are due to remains of the once extensive peripheral canalicular system.

Sixth period: endoplasmic development, second part.—Pigs 170 to 220 mm. long, approximate duration of pregnancy 105 to 110 days (fig. 12). The diversity of staining reaction is less marked than in the preceding stage, and the diversity of size of the cells is less noticeable, because in the first place the lutein cells have lost the peripheral vacuolization, while, secondly, the smaller interstitial cells of the corpus luteum have grown in size, and therefore the two types of cells so resemble each other that it is difficult to distinguish them. Fat is very slight in amount and limited to the periphery of the lutein cells, where a few granules are found. The interstitial cells of the corpus luteum are often loaded with large fat globules (fig. 13).

Seventh period: beginning retrogression.—Pigs 220 to 290 mm. long, approximate duration of pregnancy 110 days to term (fig. 14). The only difference between this stage and the preceding is that here the lutein cells frequently contain one or more fat globules larger than any previously seen, which are found near the periphery of the cell, and at first in cells near the periphery of the corpus luteum (figs. 14, 15). The oldest corpus luteum of my series (290 mm.) contains many such vacuoles.

THEORETICAL CONSIDERATIONS CONCERNING THE LIFE-HISTORY OF THE CORPUS LUTEUM.

I have purposely omitted theoretical discussion from the foregoing description, because I do not wish false analogy or faulty deduction to belittle the value of these observations as criteria for determining the age of lutein cells of pregnancy. I may be entirely wrong in ascribing to the cells which I have called type 1 an independent existence and a classification different from the true lutein cells, and in thinking that they resemble the theca lutein cells of the descriptions of Rabl, Cohn, and R. Meyer. Those who believe that the origin of the lutein cells from the theca interna alone is incontrovertibly established will simply say that, as all the cells of the corpus luteum arise from one source, what I have described are merely stages or variants of one type of cell. On the other hand, those who adhere to the now widely accepted view that both layers of the follicle enter into the formation of the lutein cells should see no difficulty in my tentative proposition that, in the sow at least, the theca cells perhaps persist partly as distinct cells throughout pregnancy. For, as I have mentioned, Rabl, Cohn, and R. Meyer have thought them to persist well into pregnancy, and Van der Stricht indeed thinks that they persist throughout pregnancy as cells of internal secretion, perhaps less active than the true lutein cells.

As to the lutein cell itself, the present findings, that the cells are apparently in a high state of organization from early pregnancy to term, would seem to give some strength to the contention that the corpus luteum has a function of importance in pregnancy. Empirically it has been shown clearly that extracts and powders of corpus luteum have a beneficial effect in certain disturbances of the reproductive system in women (see Burnam (1912) for full account and literature to date); and it has been found that extracts of corpus luteum when injected into dogs promptly cause a lowering of the blood-pressure. None of those who have worked in this field, so far as I know, have tried the effects of corpora lutea of definite age. There is, however, certain evidence that the corpus luteum during the first half of pregnancy has a different potency than in the second half, namely, the fact discovered by Fraenkel (1903) and confirmed by Marshall and Jolly (1905), Niskoubina (1909), Dick and Curtis (1912), and others, that extirpation of the corpus luteum during the first half of pregnancy is almost invariably followed by abortion. This fact, which seems so true for guinea-pigs and rabbits, has been flatly denied to hold good in animals by Daels (1908), and for human patients by Essen-Möller (1904), Graefe (1905), Flatau (1907), and Sokoloff (1913), while Puech and Vanverts (1913) propose the compromise statement that the corpus luteum is useful in an accessory way, but not absolutely necessary to the embedding and early development of the human embryo. Unfortunately for our present discussion, the experiment has not been tried on sows, which are not convenient laboratory animals. I agree with Cohn and Van der Stricht that the microscopic appearance of the lutein cell seems to favor the theory of an internal secretion of the corpus luteum, and I would add that the corpus luteum, while apparently in a high state of activity from the beginning to the end of pregnancy, shows greatly different forms of cell-structure in the earlier and later months. We may hope that this hint will be put to further test by experiment and clinical observation.

DISTINCTION BETWEEN THE CORPUS LUTEUM OF PREGNANCY AND OF OVULATION.

The history of the corpus luteum for 350 years has been a curious mingling of truth and error. Discovered by Volcherus Coiter in 1573, the corpus luteum was thought by Regner de Graaf to be an evidence of pregnancy or of previous child-bearing. Abernethy and Sir Astley Cooper swore away the innocence of a dead woman in a court of law because one of her ovaries was found at post-mortem to contain a corpus luteum. About the earlier decades of the nineteenth century it became known that every ovulation is followed by the formation of a corpus, and then arose the still unsettled discussion as to whether the corpus luteum of ovulation can be distinguished from the corpus of pregnancy. Interesting accounts of the earlier phases of this question are found in Dalton's Prize Essay of the Philadelphia Academy of Sciences for 1851, and in Taylor's "Medical Jurisprudence." Next the microscope was called to aid, with little effect. De Sinéty (1877) believed the two sorts of corpora to be exactly alike. The same statement is made by Ravano (1907). Marshall (1910) sums up his opinion in the statement that the two kinds of corpora are in the earlier stages identical, and otherwise essentially similar. Niskoubina (1909) thinks that the corpora lutea of pregnancy of rabbits contain more fat than the corpora of ovulation, but Fenger, working on the ovaries of cows, analyzed hundreds of corpora lutea, and found the fat content equal (1914). Miller (1914), in the latest publication upon this subject, holds that the corpora lutea of pregnancy (human) may be distinguished from those of ovulation by the absence of fat-reaction, of colloid degeneration, and of deposition of

calcium. It is plain that the divergent opinions upon the question are due to incomplete knowledge of the corpus luteum at all its stages. Meanwhile the clinicians are beginning to put the matter up to the anatomists anew, for instance, with such statements as that of Dannreuther (1914), that the dried corpus luteum of pregnancy is much more efficient therapeutically than the corpus luteum of ovulation.

I have sections of ovaries from about 25 uteri which did not contain embryos, many of them having been carefully examined by another investigator who was searching for early embryos. No doubt a few of them are from pregnant animals after delivery, so that the corpora lutea may not all be those of ovulation. At any rate, it can be said with certainty that the presence of embryos in the uterus is to be diagnosed by microscopic examination of the ovary. The difference between the corpus luteum of pregnancy and that of ovulation is like the difference between an army and a mob. In the corpus luteum of pregnancy there is a regularity of structure which is lacking in that of ovulation. For instance, in the latter we find cells having highly developed exoplasm side by side with others having a smooth undifferentiated cytoplasm and large fat-vacuoles in them (fig. 17). The fat-vacuoles of the connective-tissue cells are usually much larger and more numerous than in the corpus luteum of pregnancy, so that the sections are riddled with holes. It appears likely, though it can not be proven, since we have no way of determining the age of a non-pregnant corpus luteum from the slaughter-house, that retrogression sets in before the corpus is fully formed, and affects the cells in an irregular way, so that they do not all progress through the stages of their life history at one time. Whether or not there are differences of note in the first 15 days I can not say, as I have no data for corpora lutea of pregnancy in the first two weeks. After this period the two sorts of corpora lutea can be distinguished from each other.

INFLUENCE OF PREGNANCY ON THE STRUCTURE AND FUNCTION OF THE GRAAFIAN FOLLICLES.

It has been known for a long time that pregnancy interrupts the function of the corpus luteum; that in the presence of an embryo in the uterus there is normally no ovulation and therefore no formation of new corpora lutea. In animals which undergo rut or menstruation these phenomena are also interrupted by pregnancy.

To understand the causes underlying the non-occurrence of ovulation during pregnancy, we must know the life-history of the normal follicle. Fortunately this is a subject upon which there is substantial agreement between all observers. As is well known, the fully formed resting follicle consists of three layers: the membrana granulosa, of presumably epithelial origin; the theca interna, probably of mesenchymal origin; and the theca externa, of mesenchymal origin. The exact histological characteristics of the three layers vary slightly in different animals, but in the pig the granulosa is composed of 3 to 10 layers of rounded cells (the lowest layer, next the theca, is columnar) with round, darkly staining nuclei and little cytoplasm (fig. 16, *a*). The theca interna is composed of 5 to 10 layers of short, spindle-shaped cells, with moderate amount of cytoplasm and round, or oval, nuclei, not so chromatic as those of the granulosa (fig. 16, *b*). The theca externa is made up of definitely spindle-shaped cells of connective-tissue derived from the ovarian stroma (fig. 16, *c*).

Now, one of two fates awaits the unripe follicle in the course of time. It may never attain ripeness, but instead may undergo degenerative changes leading to obliteration.

The process of destruction, which is called atresia, consists of the degeneration of the granulosa cells, shrinkage and disappearance of the ovum, and filling of the cavity by enlarged cells of the theca interna, so that the atretic follicle resembles a corpus luteum, and like the latter is finally replaced by a hyaline scar. On the other hand, the follicle may proceed to ripeness, in which case the granulosa tends to range its cells in rather marked layers, and the cells of the theca interna increase in number, show mitoses, become polygonal, swell in size, and have deposited in them numerous fat granules, so that altogether they show a notable resemblance to lutein cells (fig. 18, *b*). Next, through causes not yet understood, the follicle bursts, the ovum is extruded, and a corpus luteum is formed. Should rupture not occur, atresia may take place in the ripe as well as the unripe follicle.

As one of the causes of the non-ovulation during pregnancy, it has been pointed out, especially by De Sinéty (1877), Stratz (1898), and Schulin (1881), that atresia of the follicles tends to be very marked during pregnancy. Sandes has confirmed this in the marsupial *Dasyurus* (1903). In the pig it is certainly true. I have not a sufficiently large number of non-pregnant ovaries to make a numerical comparison, but it can be stated that a great part of the larger follicles in pregnant animals are degenerating. Yet in very many ovaries of pregnancy fairly large intact follicles are found. Very interesting in this connection is the observation of Pearl and Surface (1914) that ovulation in the domestic fowl can be inhibited by the administration of corpus-luteum extracts.

It has been suggested by some that the follicles do not grow to full size during pregnancy, and that hence the crop of follicles which gave rise to the embryos *in utero* is not followed by another crop until pregnancy is terminated. This view has been studied by Leo Loeb (1906). He reports that in many of his animals the follicles went on to full size during pregnancy, but that they did not rupture, as they would in the absence of pregnancy. It is unfortunate that microscopic studies were not made, for, as pointed out by Robert Meyer, in the human ovary mere size of the Graafian follicles is a faulty criterion of their state; those which appear large and ripe may in fact be in a stage of cystic atresia.

The diameter of the ripe follicle of the sow is said by Kaeppeli to be 5 to 8 mm., and in this statement he is followed by Schmaltz (1911), but I believe that normal ripe follicles may grow much larger than 8 mm. Benckiser (1884) included in his studies on the origin of the corpus luteum a perfectly normal ripe follicle 11 mm. in diameter. I collected 24 pairs of ovaries at random, without selection except to exclude specimens containing corpora lutea and cystic formations. The largest follicles in each ovary varied in diameter from 1 to 10 mm. On microscopical examination even the largest follicle of these ovaries proved to be normal and ripe. The lower limit of ripeness is difficult to set. I have seen 3 mm. follicles which were apparently ripe; and a recent corpus luteum of ovulation may be as small as 5 mm., showing that the follicle from which it proceeded must have been no larger. In the hundreds of ovaries I have examined I have seen many such large follicles, and I have no doubt that had they been examined microscopically they would have proved normal.

As a contrast to this, in my entire series of ovaries from pregnant sows no follicles were found having an outside diameter of more than 6 mm. with two exceptions, and I did not find ripe follicles in any ovary of the series. The conclusion is simple: in pregnancy the Graafian follicles may attain or maintain a size at which, in the absence of pregnancy, ripening and rupture might occur. But they do not usually attain the larger diameters reached by follicles in the non-pregnant ovary; and when they do happen to reach large size, they are found to be either unripe or atretic.

Fellner (1909) believes that in the human ovary a few follicles may remain ripe or become ripe during pregnancy. Ravano (1907) has taken the still more advanced standpoint, based on the study of ovaries from 60 pregnant women who came to the operating table or to post-mortem during pregnancy. He found many follicles "approaching ripeness," and also thinks that he had three cases in which ovulation had occurred during pregnancy. These were merely cases in which two corpora lutea were found without twin pregnancy; and the microscopical details given are so slight that I do not think these cases are sufficient evidence on which to base such a statement as Ravano's that ovulation and corpus luteum formation subsequent to that which gave rise to the fetus occur in 5 per cent of all human pregnancies. In spite of these cases I retain the opinion that the rupture of a Graafian follicle in an ovary containing a corpus luteum of pregnancy during term is an extremely rare occurrence. Keller (1913) did not find a case in 24 human cases, Fellner (1909) in 13 cases, nor Seitz (1905) in 36. Ruge (1913) studied 106 human ovaries without finding a freshly ruptured follicle, and he thinks the presence of a recent corpus luteum excludes the possibility of the rupture of a follicle. The case which I have to report seems to be one of those classic exceptions which prove a rule.

The uterus of specimen No. 70 contained three fetuses whose crown-rump length measured 70 to 75 mm. The left ovary contained no corpora lutea; the right ovary contained 8 prominent corpora lutea about 11 mm. in diameter and a number of follicles measuring 5 mm. in diameter. Between one of the corpora lutea and one of the follicles was found a body of ovoid shape about 2 by 2 by 3 mm. in size, which presented on its surface a crater-like scar covered by a few tags of fibrin, resembling exactly the healing point of rupture of an ordinary corpus luteum, but only about 0.5 mm. in diameter (fig. 19, *a*). A section of this structure showed that it was indeed a recently ruptured follicle (fig. 20). The granulosa was several layers thick, of normal appearance, and intact except at its point of rupture, where it and also the theca were replaced by a recent scar. The granulosa was rather wavy in contour (fig. 20, *a*), and beneath it lay the theca interna, thicker than usual (fig. 20, *b*). If I interpret the appearance aright, neither layer showed signs of conversion into lutein cells. I believe that this unusual specimen is due to an accidental rupture of a Graafian follicle, probably by pressure between its neighboring growing follicle and corpus luteum.

ABNORMALITIES OF THE LUTEIN TISSUE.

An interesting anomaly of the ovary is partial accessory lutein-cell formation, to which attention was called by R. Meyer (1913). This consists of the formation, during pregnancy, of lutein cells in atretic follicles or even in ripe follicles, which in some human ovaries is said to go so far that a full corpus luteum may be formed which is finally indistinguishable from the true corpus luteum proper to the pregnancy, which is found in the same ovary or its mate. This phenomenon, at least in its advanced state, must be very uncommon. In the sow I have seen a case of what is apparently the same partial lutein formation in a normal ripe follicle, not during pregnancy, but in the presence of a corpus luteum of ovulation.

The right ovary of specimen No. 136 contains 4 corpora lutea 5 mm. in diameter, which appear on section to be young corpora lutea of ovulation. In addition there is a follicle 10 mm. in diameter, to be described. The left ovary contains 3 corpora similar in gross appearance to those of the right ovary, except that one of them is slightly cystic. On section of the large follicle in the right ovary, it is found that over almost the entire circum-

ference the wall presents, as would be expected, the structure of a normal unripe follicle. At one point, however (fig. 21, *a*), for a space of 3 mm. the whole theca interna is doubled or tripled in thickness, its cells show the appearance of ripeness, and have begun to invade the granulosa (fig. 22, *a*). The granulosa cells, in turn, are 20 to 30 microns in diameter and many of them have vesicular nuclei with prominent nucleoli; they are filled with fat-vacuoles, and some of them have in their cytoplasm the ring-formations of young lutein cells. In short, the granulosa cells are turning into lutein cells (fig. 23).

Seitz (1905) has emphasized the transformation of theca-interna cells of atretic follicles into lutein-like cells as a physiological phenomenon in pregnancy. While I do not consider this process as uniformly present in the sow, as Seitz maintains it is in the human, still we do occasionally find follicles lacking the granulosa, but with the theca interna cells full of fat-vacuoles and enlarged just as in ripe follicles. It is hard to see how it is to be decided whether these were normal ripe follicles at the beginning of pregnancy, which are merely becoming atretic, or whether they were formerly atretic follicles in which the formation of theca-lutein cells is taking place, as Seitz would have it.

Here we come to the border-line between normal and pathological anatomy of the ovary. While my specimens of ovarian cysts were not collected with a view to formal study, still I shall risk presenting a few incidental observations in the hope of calling attention to the unusually promising opportunity offered by the sow's ovary for the study of the pathology of the Graafian follicle and the corpus luteum. Cysts are extremely common, are often multiple, and are frequently found in ovaries containing normal corpora lutea of ovulation, so that comparisons can be made. It needs only time and patience to collect a great number, and the result would undoubtedly give us explanations of much that is obscure concerning these tumors.

In glancing over the 13 specimens of ovarian cysts lined by lutein cells which I have collected, it at once appears that they fall into two classes. First, there are cases in which one of a crop of corpora has merely retained its original cavity beyond the normal time, the cavity has become fixed, and may have become much enlarged. Second, there are cystic cavities in the ovary which are lined by lutein cells, but which we can not as surely say came from the corpora lutea, as they may merely represent atretic follicles in which lutein-cell formation has taken place. One's view of the origin of these cells will depend entirely upon the view of the origin of the lutein cells of normal corpora. As will have been gleaned from this paper, the writer has tentatively come to the belief that the true lutein cells are derived from the granulosa cells, but that the theca interna gives rise to cells resembling lutein cells, which seem in part to remain as special cells in the fully formed corpus luteum, but most of which are lost, either by reverting to connective-tissue cells of the ordinary kind or by becoming themselves genuine lutein cells. On this theory, we should have the following kinds of lutein-cell cysts:

I. Arising in corpora lutea which have remained cystic or have undergone cystic degeneration.
II. Arising in follicles:
  a. Accessory lutein-cell formation from both layers of normal follicles, as described by Meyer.
  b. Accessory lutein-cell formation from the theca alone, as in atretic follicles.

It is of clinical importance to know something about the life-history of lutein-cell cysts—for instance, whether such a cyst may persist and by its activity inhibit ovulation, as in certain women, in whom persistent corpora lutea seem to cause sterility. Now, the

lutein cells in cystic tumors are not often as well preserved as in normal tissue, but I believe that in all the specimens in hand the lutein cells are of the same age as those of the normal corpora in the same ovary. I have not seen lutein-cell cysts containing active-looking cells of different age from the corpora lutea present. Presumably, then, the lutein cells of cysts are as transient as normal lutein cells, and in cases where the cystic formation persists, the lutein cells lining it probably revert or disappear, so that finally the cysts can not be distinguished from an old Graafian follicle cyst.

In the 128 specimens from pregnant sows of which I have record, there was only one case of lutein-cell cyst. In the same number of non-pregnant ovaries, containing corpora lutea of ovulation, we should find 5 or 10 lutein-cell cysts. For comparison, I have looked up the cases indexed as corpus-luteum cysts in the records of the gynecological service of the Johns Hopkins Hospital. There were 19 cases available, all discovered at operation for other conditions. One patient had passed the menopause (61 years); the others were from 16 to 42 years.

8 had never been pregnant.
4 had their last child or miscarriage 6 or more years before.
5 had their last child or miscarriage 22 months to 4 years before.
1 had miscarried 4 months before, at the second month.
1 had miscarried 2 weeks before, at the sixth week.

Apparently, then, the corpus luteum of pregnancy is a comparatively less frequent seat of cysts than that of non-pregnant animals, a fact in accord with the general rule that abnormal alterations are less frequent in organs exercising a needed function.

MIGRATION OF THE OVUM IN THE SOW.

Since the uterus of the sow is bifid nearly its whole length, it is very easy to count the number of fetuses on each side. When this is done, it is often observed that there are more pigs on one side of the uterus than there are corpora lutea in the corresponding ovary. In a series of 117 uteri, I found 28 in which there was 1 more pig than corpora lutea on a given side, 13 cases with 2 more pigs than corpora lutea on one side, and 2 in which the pigs numbered 3 more than the corpora lutea of the corresponding ovary.

This phenomenon may be explained in three ways: (1) corpora lutea may not have formed at the site of the follicle which gave rise to the supernumerary pigs; (2) there may have been two or more ova in one follicle, which therefore produced two or more embryos, but only one corpus luteum; (3) one or more ova may have crossed the abdominal cavity and entered the opposite tube (external migration), or passed down to the junction of the uterine horns on its own side and into the opposite tube from below (internal migration).

(1) The failure of a corpus luteum to form at the site of a ruptured follicle is not unthinkable, but must be very rare. In hundreds of sows' uteri I have never seen a case of pregnancy without corpora lutea; nor do I know of any really unexceptionable cases reported from the human or any other of the mammalia which give birth to a single infant, in which such a phenomenon would be more easily detected. Fellner (1909) has mentioned one case in a woman who died on the day of delivery, Ravano (1907) cites four, also from women practically at term, and Miller (1914) one from a case of eclampsia. Although these cases are of interest otherwise, the absence of a corpus luteum at term can not be taken as evidence that one had not been present earlier in pregnancy, especially since all these cases were complicated by disease.

(2) In the sow, however, I have found a uterus in which there were 5 fetuses, but only 4 corpora lutea in both ovaries. Such a case, if our first hypothesis be excluded, can be explained only by the second, namely, that two of the pigs originated from a polyovular Graafian follicle, and this latter explanation is based on anatomical facts. Follicles containing more than one ovum have been known for many years, and have been recorded from man, the cat, dog, sow, certain bats, and other animals. Ancel (1903) thinks they are especially common in the dog, in which he has found follicles with 2, 3, 4, 5 ova. Arnold (1912), in an interesting report with review of the literature, describes a human case in which a large proportion of follicles were polyovular, some of them having as many as 18 ova. The anatomical origin of the condition is still obscure. The question arises whether the phenomenon is sufficiently common to account for the fact that in swine 37 per cent of uteri have more pigs in one horn than there are corpora lutea in the corresponding ovary. Schmaltz (1911) states that polyovular follicles are seen in almost every preparation of the sow's ovary, sometimes having as many as 6 ova, 4 to a follicle being frequent, but he thinks that such follicles are usually doomed to become atretic and rarely attain maturity. In sections I personally have found only 2 polyovular follicles, one of them with 2, and the other with 3 ova, and these follicles were both small and undeveloped. The members of a class in histology were requested to watch for the condition when studying the ovary of the sow, and one of the students found and showed me 2 ova which he had discovered in a large ripe follicle. The conclusion is that some of the 43 cases under discussion may have been due to the fertilization of ova from polyovular follicles, but that the latter certainly do not occur frequently enough to explain all the cases, since for this it would be necessary for at least one follicle to be polyovular in one-third of all the groups of follicles maturing at once.

(3) On the other hand, migration of the ovum is a well-attested fact, in the human subject, and has been produced experimentally in animals by Leopold (1880), who excised one ovary and the opposite tube, and found that the animals could still become pregnant. Howard A. Kelly performed the same operation in a human patient, for the cure of disease, and the woman later became pregnant. Other interesting examples have been mentioned by J. Whitridge Williams, who found the corpus luteum in one ovary and the embryo in the opposite tube, in 5 out of 30 carefully recorded cases of extra-uterine pregnancy. These are all cases of external migration. The occurrence of internal migration has never been conclusively proven. The frequency of external migration of the ovum is difficult to estimate in the human subject, since it is demonstrable only in the presence of some abnormal condition, such as the lack of one tube and the opposite ovary, a bicornate uterus, an extra-uterine pregnancy, or the like. Mayrhofer (1876) estimates tentatively that migration must occur at least once in every ten ovulations in the human female.

That it can take place in the sow I think is proven by four uteri of my series, in each of which one ovary contained no corpora lutea, and yet in two of the cases the side of the uterus corresponding to the ovary without corpora lutea contained 1 fetus, in the other two cases 3 fetuses. In all four cases the total number of corpora lutea in both ovaries accounted for the total number of pigs in both sides of the uterus. In all likelihood we can explain most of our cases by external migration. The point which I wish to bring out is not that migration is a possibility—that has been shown many times—but I want to emphasize its great frequency. For every time it can be demonstrated in the sow, there must be many more times when it can not be detected; for instance, when ova migrate from both ovaries, and hence the condition is not apparent. It is a very conservative estimate if we suppose that one or more ova migrate in 50 per cent of all ovulations in the sow. In a sense, the term

migration is a misnomer, for the ovum does not make any great journey to reach the opposite tube. I have not had the opportunity to study the relations of the pelvic organs in an adult sow, but in large fetuses the ovaries may be quite close to each other; I have even found them touching. It is likely that the fimbriæ of the Fallopian tubes, which in the sow are widely spreading and patulous, frequently reach both ovaries, and hence make it a matter of chance which tube receives a given ovum.

The question of the migration of the ovum has two aspects of immediate practical interest. To the gynecological surgeon it is important to know that the extirpation of one tube and the opposite ovary will not necessarily cause sterility. For the biologist the subject brings up certain questions concerning the determination of sex, which will be mentioned briefly. It is a very ancient theory that the production of two sexes of offspring and their practically equal distribution in number are due to the formation of males by one ovary, of females by the other, the left ovary usually being honored by the ascription of female-producing potencies. This simple hypothesis is capable of proof or disproof by numerous methods, which have not been wanting a trial, the most recent of such experiments being those of G. H. Parker (1914), who adopted a very neat and ingenious plan of experimentation. The method was to take an animal possessing a notably bifid uterus, namely, the sow, and count the number of unborn pigs on each side with reference to sex. Parker recognized the possible disturbing effect of migration of the ovum, though I think to a far less degree than the facts warrant; and therefore he took large litters, and omitted from his counts the pigs in the middle of the uterine horns, which may be thought most likely to be the mixed product of the uterine horns, and counted only the two fetuses next to each ovary and the two next the junction of the horns. The result, from the tabulation of 1,300 pairs of fetuses, gave an almost absolutely equal distribution of the sexes on the two sides. Now, at first sight it might seem that the great frequency of migration of the ovum, which I have shown to exist, renders Parker's conclusions false, since they are based on the general assumption that the embryos on one side of the uterus come from the corresponding ovary. But, on the other hand, if it is true, as I believe, that the embryos in either horn of the uterus are an inextricable mixture of the products of the two ovaries, then Parker's figures can only be explained by the far-fetched assumption that exactly 50 per cent of the ova migrate, or else that both sexes are equally represented in each ovary; the latter being of course the conclusions already reached by Parker.

CONCLUSIONS.

In the foregoing paper the writer has given an account of the histology of the corpus luteum of the domestic sow, remarking the presence of cells differing from the typical lutein cells.

A description is given of the canalicular apparatus and granules found in the lutein cells, and it is shown that these structures undergo progressive changes during the course of pregnancy.

The microscopic appearance of the corpus luteum is described as it varies with the advance of pregnancy.

The corpus luteum of pregnancy is distinguished from that of ovulation by the more regular and uniform morphology of the former, and the greater infiltration of fat in the latter.

During pregnancy the Graafian follicles do not undergo the process of ripening, or change of the theca interna which is preparatory to rupture.

External migration of the ovum is a normal and very frequent occurrence in the sow.

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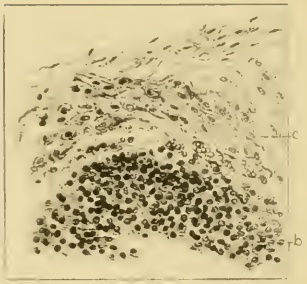

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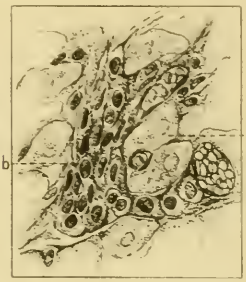

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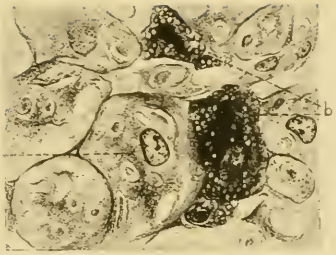

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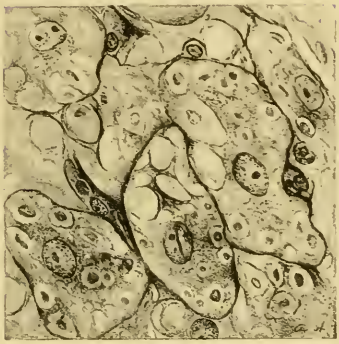

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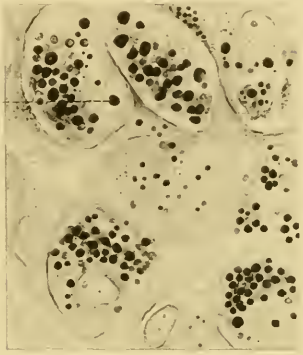

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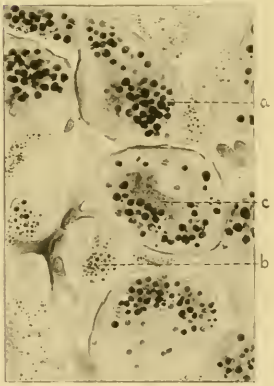

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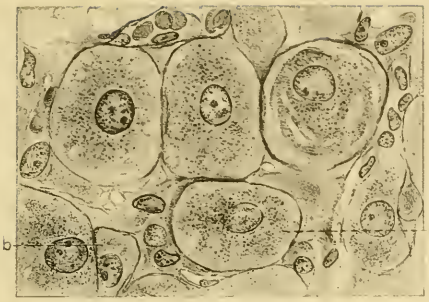
1. The wall of a recently ruptured Graafian follicle, showing the granulosa intact. Hematoxylin and eosin. × ca. 100.
   (*b*) Granulosa. (*c*) Theca interna.
2. Additional cells of corpus luteum, type 1, Mallory's stain. × 400.
   (*a*) Lutein cells. (*b*) Additional cells, type 1.
3. Additional cells of corpus luteum, type 2, Mallory's stain. × 650.
   (*a*) Lutein cell. (*b*) Additional cells, type 2.
4. Corpus luteum, first period, Mallory's stain. × 650.
5. Corpus luteum, second period, Mallory's stain. × 650.
6. Corpus luteum, second period, osmic acid stain. × 650.
   (*a*) Droplet of fat inside one of the peripheral vacuoles.
7. Corpus luteum, third period, Mallory's stain. × 650.
   (*a*) Lutein cell containing ring-form of canaliculi. (*b*) Lutein cell containing cleft-like canalicular apparatus.
   (*c*) Chromatic granules.
8. Corpus luteum, fourth period, Mallory's stain. × 650.
9. Corpus luteum, fourth period, osmic acid stain. × 650.
   (*a*) Fat-globules in a lutein cell. (*b*) Fat-globules in a connective tissue cell. (*c*) Chromatic granules.



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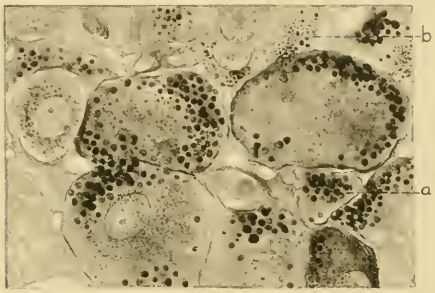

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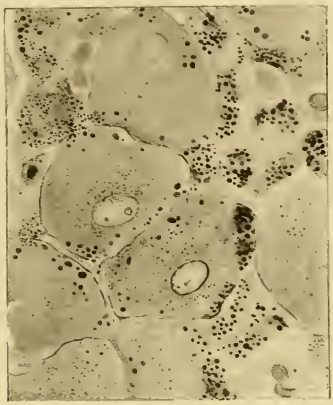

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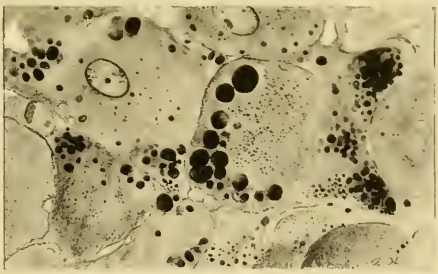

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10. Corpus luteum, fifth period, Mallory's stain. × 650.
(*a*) Lutein cell showing no peripheral vacuoles. (*b*) Additional cell, type I.

11. Corpus luteum, fifth period, osmic acid stain. × 650.
(*a*) "Additional" cell containing large fat-globules.
(*b*) Connective tissue cell containing minute fat-granules.

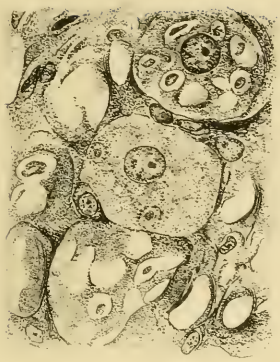
12. Corpus luteum, sixth period, Mallory's stain. × 650.

13. Corpus luteum, sixth period, osmic acid stain. × 650.

14. Corpus luteum, seventh period, Mallory's stain. × 650.

15. Corpus luteum, seventh period, osmic acid stain. × 650.

16. Wall of unripe Graafian follicle, hematoxylin and eosin. × 400.
(*a*) Granulosa. (*b*) Theca interna. (*c*) Theca externa.



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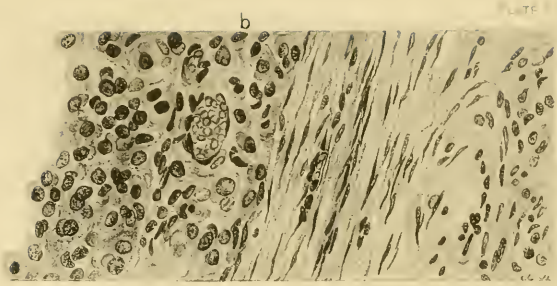

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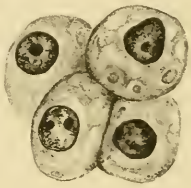

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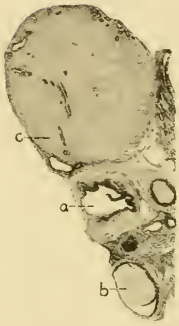

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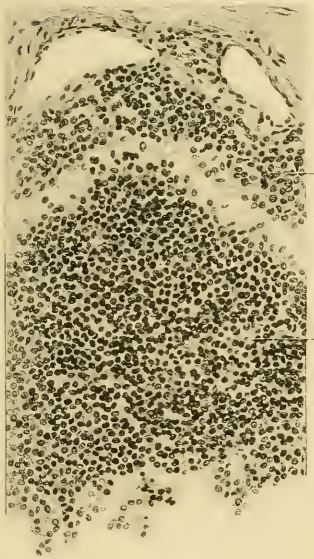

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17. Corpus luteum, of ovulation (non-pregnant sow), hematoxylin and eosin. × 650.
18. Wall of ripe Graafian follicle, hematoxylin and eosin. × 400. (*b*) Theca interna.
19. Specimen No. 70, showing a Graafian follicle ruptured during pregnancy. Hematoxylin and eosin. × 3.
(*a*) The ruptured follicle. (*b*) An unruptured follicle. (*c*) A corpus luteum of pregnancy.
20. Wall of follicle shown in Figure 19. Hematoxylin and eosin. ×. ca. 100.
(*a*) Granulosa. (*b*) Theca interna.
21. Specimen No. 136, a Graafian follicle showing partial accessory lutein-cell formation. Hematoxylin and eosin. × 3.
(*a*) Point at which the accessory lutein formation occurs.
22. Showing the area marked *a*, Fig. 21, enlarged 70 diameters. Hematoxylin and eosin. × 70.
23. Four cells of the granulosa of the same specimen, showing ring-like vacuoles in the cytoplasm like those seen in lutein cells. Mallory's stain ×800.

CONTRIBUTIONS TO EMBRYOLOGY, NO. 6.

TRANSITORY CAVITIES IN THE CORPUS STRIATUM OF THE HUMAN EMBRYO.

By Charles R. Essick.

With three plates.

TRANSITORY CAVITIES IN THE CORPUS STRIATUM OF THE HUMAN EMBRYO.

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INTRODUCTORY.

The human embryo, during the seventh week of development, possesses two bilaterally symmetrical cavities in the substance of the corpus striatum. Since one lies nearer the midline than the other, I have called them cavum mediale corporis striati and cavum laterale corporis striati. The former is deeply placed in the striate body, while the latter occurs nearer the surface of the brain, at times separated from the pia mater by a layer of nervous tissue only a single cell in thickness. In all of the embryos in the collection of the Carnegie Institution of Washington, ranging from 15 to 20 mm., crown-rump measurement, one or both of these cavities are present, while above these measurements they appear with diminishing frequency; so that in all of the specimens under 15 mm. (measurement in formalin) and all over 24 mm. evidences of them are lacking.

Undoubtedly the ephemeral character of these cavities and their similarity to artifacts account for the fact that they have heretofore escaped notice. The study of human embryological material can not always be followed in specimens that have been fixed alive; more often one must be content with tissue that has begun to macerate. It is very natural, then, to regard a rent in tissue as a fault in technique, especially in the central nervous system, where shrinkage is one of the most difficult things to avoid in preparing and mounting serial sections.

THE CELL-CONTENT OF THE STRIATE CAVITIES.

Inasmuch as the identification of both mesial and lateral cavities is based on their contents, it may be well to describe the peculiar cells, foreign to the nervous tissue, which occupy both cavities in large numbers whenever found in the striate body. They must be regarded as the best proof of the normal occurrence of spaces in the human brain. From the moment one of these striate cavities makes its appearance as an irregular break in the continuity of the nervous tissue, until its complete disappearance, it is inhabited by large amœboid cells having the power of phagocytosis. Study of the whole embryo and its membranes shows that these cells are not peculiar to the cavities; for the same cellular elements may be seen in the mesenchymal spaces, especially when of loose texture. Enormous numbers may be found in the younger chorionic villi; along the umbilical cord many wander near the surface; multitudes are present everywhere in the loose mesenchyme around the central nervous system, especially near the base of the fore-brain; they occur with less frequency along the aorta and in the mesentery.

These widely distributed cells have been figured by many observers—usually in connection with the formation of the blood. Hofbauer, Grosser, and Minot have illustrated the cells in the chorionic villi of human embryos of the first months of development. Hofbauer (**5**, p. 28) first called attention to specific round cells appearing in the human placenta toward the end of the fourth week of pregnancy. Describing in detail these "vakuolären Zellen," he called attention to the many points of similarity to the plasma cell—*i. e.*, the eccentric nucleus with its rich chromatin network and its surrounding clear zone.

According to Grosser (**3**, p. 224): "Regel-mässig finden sich in Zottenstroma bei Eiern des ersten Schwanger-schaftsmonate, grosse, protoplasma-reiche Zellen, auch die in letzter Zeit wieder Hofbauer aufmerksam gemacht hat, deren Bedeutung aber noch unklar ist."

These two authors are at a loss to explain the existence of the cells, while Minot (**8**, p. 498 ff.) regards them as erythrocytes which have wandered into the mesenchyma, and, remaining there, have swollen by imbibition and are undergoing degeneration by vacuolization of their protoplasm. In figure 361 this author has illustrated "degenerating blood-cells" in the chorion of embryo 350—an embryo included in this study. Such an interpretation finds little or no support from my observations. The vacuolization of the protoplasm suggests degeneration, but such an hypothesis is overwhelmed by many other factors pointing to a very active life—*i. e.*, mitosis, phagocytosis of foreign material, evidences of amœboid movement, and lack of hemoglobin. Then, too, his figure 361 gives a false impression of the relative size of a normal erythrocyte and these large phagocytic cells (cf. figs. 13, 15, 18, 22, and 31). The former may easily be accommodated in the body of the latter, and only the largest red cell that one can find shows any approach to the size of the phagocyte. Most observers have regarded these colorless cells as the ancestors of the blood elements, at least whenever they are found in the body of the embryo itself. O. van der Stricht (**11**) includes under the class of phagocytes "leucoblasts" which correspond exactly to these cells, so widely distributed through the whole ovum. Saxer (**10**) derives them from the common vascular and blood anlagen, which he differentiates from connective-tissue elements. From these primary "Wanderzellen" of Saxer descend a series of cell-forms, including giant cells, wandering cells of I, II, and III orders, erythrocytes, and colorless cells. The Wanderzellen persist into adult life and continue their blood-forming powers in the bone marrow and adenoid tissues.

Maximow (**6**) holds that the embryonic ancestor of this cell is the mesenchyme out of whose network it is gradually separated to become a free-moving cell. With the exception of the extremities and gill-arches, he finds these "Wanderzellen" everywhere in the loose mesenchyme, "allermeisten sich in Kopfmesenchym in der Nähe der Gehirnwand, vornehmlich an ihrer ventrolateralen Seite befinden."

For a long time, morphologically similar cells have been recognized in the adult as playing an important rôle in inflammation. It has recently been shown that these probably have no relationship to the normal blood elements. Metchnikoff (**7**) has given the cells of this class the name of "macrophage." This term has been adopted here because of its application by recent observers to a group of cells normally inhabiting the connective tissues, serous cavities, and hematopoietic organs. The remarkable peculiarities of the adult cells characterize them even in the very young embryo. This will be seen from the following description, for although they are wholly unlike the young and incompletely differentiated tissue in which they are found, they correspond with striking exactness to those of the adult. A very clear physiological relationship between the widely distributed adult cells has been demonstrated by Dr. Evans (**2**) by means of vital stains; his results have led me to include these cells in the same class because of their morphological characteristics.

While Hofbauer's use of stains is hardly analogous to their introduction as vital dyes, it is interesting to note that by teasing living chorionic villi in solutions of neutral red, he found (p. 124), "Wahrend alles (darunter auch das Syncytium) ungefärbt blieb oder einen leichten Stich in Rosa annahm, treten die 'vakuolären' Zellen der Zotte tief saturiert gefärbt und beherschen die Bildfläche." Plato (**9**) showed that cells engaged in phagocytosis are particularly prone to stand out brilliantly in supravital stains because of the deep tingeing of their phagocytized contents. Such evidence would account for Hofbauer's finding.

Several characteristics, easily recognized, permit the inclusion in the same tissue class of the large mononuclear cells found so extensively distributed in the membranes of the embryo, in the umbilical cord, in the mesenchymal spaces, and in the cavities in the corpus striatum.

The average cell-body of the younger embryo measures from 10 to 13μ, while in the older specimens it ranges from 16 to 19μ. This increase in size accompanies roughly the growth of the embryo, although there are always smaller cells belonging to this group (figs. 19, 25, 30). Thus it may be seen that the largest red cell is several times smaller than the largest macrophage, and the former may be easily accommodated inside the latter. Comparison of the measurement of many cells from chorion and cavum corporis striati shows them to be of the same size, when one is fortunate enough to get the membranes and embryo mounted on the same slide; even when mounted separately there is very little discrepancy in favor of cells in either position.

The shape of the cell depends largely on its environment. When free it tends to assume a spherical form (figs. 13, 17, 18, 20, 21), but in places where it can find support it sends out long processes which are undoubtedly pseudopodia (figs. 15, 22). To obtain specimens of cells with extended pseudopodia the fixation must be prompt; failure to procure such pictures of moving cells is best explained on this basis. The shape is often irregularly oval, due to the ingestion of foreign bodies, particularly erythrocytes (figs. 26, 27). At times the macrophages grow in clumps of from 20 to 50, forming a mulberry-like mass. This may occur in either medial or lateral cavity of the corpus striatum, and is well illustrated in figure 12 for the cavum laterale. Here the cells have become flattened by the pressure of their neighbors and in section seem to be forming a loose membrane the elements of which are polygonal in outline.

The cells have a limiting membrane, very thin but definite; although it is almost impossible to defend the view that the phenomenon illustrated in figure 12 is not an instance of protoplasmic bridges connecting several cell-bodies. Large numbers of cells are extremely verrucose (figs. 23, 25, 26). Examination of the cavities where these cells are found reveals a great deal of débris simulating protoplasm. This is undoubtedly coagulated proteid which has accepted the counterstain and has precipitated on the surface of the macrophages. Figures 13, 18, 19, and 20 represent more faithfully the delicate cell-membrane when the cell has withdrawn all of its pseudopodia.

The protoplasm is finely granular and is delicately arranged throughout the cell-body in anastomosing strands which give an appearance of lacework. These trabeculæ vary greatly in thickness and surround vacuoles within the cytoplasm. In the younger cells these vacuoles are usually small, but at times they may be larger than the cell-nucleus itself. Where the protoplasmic strands reach the cell-membrane they reinforce it in an irregularly shaped mesh, such as may be seen in the illustrations of cells from chorion or brain. This appearance is brought about by the extreme vacuolization which extends throughout the whole cell, and as a result the finely granular protoplasm is heaped up in the interstices between the vacuoles and the cell-wall. Great numbers of macrophages may be found with foreign material included within their cell-bodies; the power of phagocytosis is one of the most interesting phenomena exhibited by these cells. Although cells containing ingested matter are rarely found in the chorionic villi, the cells everywhere in the body of the embryo may contain phagocytized matter. The erythrocyte forms the foreign material most frequently recognized within the phagocytes. An extravasation of red corpuscles in the young embryo has occurred in most of the material studied; this is probably due to the fact that it was subjected to high pressure in abortion. The presence of large numbers

of erythrocytes free in the tissue-spaces is not unfortunate, since they have stimulated these macrophages to unusual activities whenever it occurred in their neighborhood. Embryo 406 furnishes many examples of red cells ingested by these large mononuclears in the cavities of the corpus striatum. Figure 26 is particularly interesting, as it illustrates a remarkable phenomenon, namely, the division of a cell with a large mass of foreign material in its cytoplasm. One of the asters is found on the edge of the cell, while the other lies beneath the ingested nucleated red blood-cell, and could not be drawn without confusing the picture.

Figure 27 shows the beginning digestion of the erythrocyte. Here the large macrophage from the cavum laterale corporis striati contains two smooth spheroidal bodies, stained decidedly pink, yet not as deeply colored as the erythrocyte contained in the dividing cell (fig. 26). Erythrosin has a marked affinity for cells containing hemoglobin, and it here reveals these inclusions as two homogeneous globules. There is no evidence of a nucleus in either of these two hemoglobin-containing fragments. Embryo 74 contains cells which show the last stages of erythrocyte digestion (fig. 28). Here the macrophages contain a few granules of brown pigment—not very unlike the large phagocytic cells known as "Herzfehlerzellen," in the sputum of patients suffering from chronic passive congestion of the lungs. It is very certain that long after the embryonic heart has stopped beating and erythrocytes have been forced out of the capillaries, these huge amœboid cells continue to be actively engaged in the ingestion of foreign bodies. Even up to the time of fixation, apparently, these cells are functioning, if mitotic division may be used as an index of a living cell. It is easy to understand how some of these red cells may be reduced to brown pigment granules when one considers the length of time which often elapses between the separation of the placenta from the uterine wall and the fixation of the specimen. Careful, prolonged search has been made to determine the presence of nervous tissue in the bodies of the phagocytic cells inhabiting the corpora striata. In no instance was it possible to identify with certainty any of the inclusions as neuroblasts.

Most of the cells contain a single nucleus, for the most part eccentrically placed. It is large, varying from 4 to 6μ in the younger embryo and from 5 to 8μ in the older, and has a distinct nuclear membrane. The rich chromatin network with its many enlargements is beautifully shown in the specimens stained with hemotoxylin. Many of the cells have nucleoli attaining at times a diameter of 2μ. These are then the center of a radiation of chromatin threads. The nucleus may be irregular in shape, as shown in figures 12, 13, and 28, but in most instances it has a smooth contour. The irregular nuclei belong to cells which have begun to show signs of degeneration. As they grow older they gradually lose their power of staining and finally disappear. The eccentricity of the nucleus is a most striking peculiarity. One commonly sees the nucleus in direct apposition to the cell-membrane. Perhaps the only instance of a lack of similarity between the macrophages of the embryo and those of the chorionic villi is to be found in the method of regeneration.

Everywhere in the mesenchymal spaces, and especially in the cavities in the corpus striatum, it is not difficult to find mitotic figures in these phagocytes (figs. 24, 25, 26); in contrast to this one very rarely comes upon a dividing macrophage in the chorionic villi. Figure 16 is an illustration of such an instance. It must be noted that all of the characteristics described for the protoplasm are retained during mitosis—loose texture, vacuolization, and engorgement with foreign particles. Cells with two nuclei have been observed in the brain cavities, and the peculiar protoplasmic strands which sometimes bridge the gap between them are illustrated in figure 29. The size of the nuclei, as well as the presence of a nucleolus, in only one of them, makes it probable that we are dealing with direct division

in these cells, although there is no indication of a constriction of the cell-body. An oddly shaped nucleus has been pictured in figure 30; here the form is concavo-convex, with the convex surface near the cell-membrane. This illustration is inadequate in so far as it gives one the impression of a kidney-shaped nucleus.

Unfortunately, not all of the material at my disposal has been exhausted in an effort to establish a life-history for these macrophages. Many puzzling questions have been presented by the distribution of the cells; yet a few general conclusions may be drawn from these observations. With few exceptions, in the youngest human embryos the preservation has precluded a careful cytological study; and often it is with reluctance that one admits the failure to discover these cells in positions where one expects to find them.

The chorionic villi in the very youngest ova seem to be devoid of the large vacuolated cells first noted by Hofbauer. Embryos of 2 mm. (No. 391 in this collection) possess a few of these cells sparsely scattered about the villi and a few in the chorion itself, but none in the body stalk nor in the embryo. In the larger specimens parts of the villi are entirely free from these independent cells, which are found in large numbers in other portions of the villi, chorion, and even the body stalk (No. 186, 3.5 mm.; No. 164, 3.5 mm., and No. 463, 3.9 mm.), but the mesenchyme around the aorta or brain shows none of the typical large vacuolated cells so common in the membranes. After the embryo has passed 5 mm. these cells may be seen in the mediastinum and around the brain; the ease with which they are found in the loose mesenchyme increases with the growth of the embryo. As noted by Hofbauer, they gradually disappear from the villi as the mesenchyme takes on a more fibrillar character. Hence in the older portions of the chorionic villi—*i. e.*, those in which the larger vessels and denser framework exist—relatively few of these phagocytic cells may be found, even in the younger embryos. In the later stages they disappear from the placenta entirely.

Certain embryos contain a much larger number of macrophages in their placentæ than others of a similar stage of development. This peculiarity, as we shall see, holds true for the cavities in the corpus striatum, where there is the same tendency to extreme variation in the number of the cells present. The presence of large numbers of macrophages in one locality is not necessarily accompanied by a similar increase in the other; thus in embryo 350 the placenta (fig. 14) contains very many cells, while the cavum mediale corporis striati contains only a few (fig. 2); in embryo 22, on the other hand, the conditions are exactly reversed.

In order to determine the origin of these cells more accurate methods of investigation than the mere study of routine serial sections must be employed. Hofbauer's attention was directed to their mode of origin by Marchand; these workers believed them to be descendants of the connective-tissue elements. A section taken from embryo 800 might be given in support of their view. The character of the cells of the layer of Langhans is not very unlike that of the younger macrophages, and it is possible that the macrophages of the villi may arise from that layer directly. The cells, when in the body of the embryo proper, apparently preserve their specificity and give rise to younger generations by mitotic division.

These cells, then, whose presence in the striate cavities argues strongly for the functional existence of bilateral spaces, should be considered as of the type of extra-vascular phagocytes. They correspond in morphology to the Hofbauer cells of the young chorionic villus, to the Wanderzellen of Maximow and Saxer, and to the macrophages of later writers.

THE OCCURRENCE OF THE TWO STRIATE CAVITIES.

In searching through the literature for illustrations of these cavities only one could be found which unquestionably had reproduced either of the spaces in the corpus striatum. His (**4**, p. 124, fig. 83) has published a photomicrograph of the fore-brain of a 16 mm. human embryo *Se*, in which the two halves of the brain were not sectioned symmetrically, so that different levels appear on the two sides of the median line. Fortunately, on the left side the cavum laterale corporis striati occurred in the plane of section. It is roughly piriform, the pointed extremity being directed toward the cerebral ventricle, while the blunt end approaches the surface of the striate body. This illustration of the lateral cavity is very similar in its position and size to those illustrated in figure 7, which is photographed from embryo 409, a specimen of exactly the same length as *Se*. The lateral cavity usually develops before the medial, so that it is safe to predict that the His embryo would show another cavity more deeply placed in the striate body if the plane of section had not been so oblique.

The accompanying list of embryological material from the Carnegie Institution of Washington includes all the specimens from 15 mm. to 23 mm. (crown-rump length) which permit of histological study. With but one exception, evidences of one or both sets of cavities have been found in the corpus striatum.

Crown-rump length in mm.	Collection No.	Crown-rump length in mm.	Collection No.	Crown-rump length in mm.	Collection No.
14	144	16	74	20	349
15	719	17	296	20	128
15	350	17	576	20	240
15.2	423	17.2	424	20	22
15 5	390	18	432	21	460
16	43	18.5	431	23	453
16	406	19	293	23	382
16	409	19	229	24	455

The cavities in the corpus striatum fall into two groups—one appearing very near the lateral surface of the brain, the other occupying a medial position within its substance. Generally each is but a single cavity, and all of the smaller diverticula communicate with the main cavity. Either, however, may be represented by multiple cavities wholly unconnected with one another, yet so close as to be separated only by a thin partition of nervous tissue. As it lies deep in the striate body, the medial cavity tends to be more smooth-walled than the lateral. The latter is frequently traversed by numerous blood-vessels having a thin layer of neuroblasts adhering to their walls; small strands of nerve-cells stretch like spider-webs from one wall to another. In addition to the cavum mediale and cavum laterale an intermediate group is present in one specimen, situated midway between the two. In all of the specimens studied the medial group appears in younger embryos than does the lateral, and disappears first in some of them. There are embryos of 24 mm. in which both cavities are still well developed.

No direct communication between these cavities and the vascular system could be made out. In none of the four injected embryos included in this study (No. 390, 15.5 mm.; No. 424, 17.2 mm.; No. 460, 21 mm.; No. 382, 23 mm.) was there any tendency for the injected mass to flow out into these spaces, although vessels containing granules of injection coursed directly through the cavity. In one instance (embryo 460) a small amount of India ink backed into the cavum laterale from an extensive subpial extravasation. When erythrocytes have been found in these spaces the cavity has shared in a generalized extravasation of formed elements throughout the entire head.

THE CAVUM MEDIALE CORPORIS STRIATI.

If one neglect embryo 144, on account of its being given its measurement after it was mounted on the slide, whereas all of the other specimens were measured before embedding, we find that the cavum mediale makes its earliest appearance in embryos of 15 mm. (No. 719 of this series). Deep in the substance of the striate body, in close proximity to a blood-vessel, may be found a slight separation of the nervous tissue. Although not unlike an artifact, it exists in exactly the same place on the two halves of the brain—in other words, it is bilaterally symmetrical. In the transverse sections of this embryo it appears, under low magnification, as a less dense area 150μ long and 65μ broad. A single 40μ section includes the major portion of the entire space, and it is terminated abruptly in the sections on each side of it. Closer observation reveals strands of neuroblasts bridging the gap, here a single cell stretching across the cleft, there a group of young neuroblasts extending from one wall to the other. In the irregular fissure thus produced are found many macrophages, their cell-bodies almost filling the space formed by the separation of nerve-cells. Unfortunately, a careful cytological study is not possible, owing to the thickness of the section and the dense stain. No formed elements could be made out in the bodies of these large phagocytes, although it seems likely that an extensive destruction of nervous tissue is taking place. The macrophages are not found outside of the space (*i. e.*, among the cells making up the adjacent nervous tissue), but lie among the nerve-cells which bridge the newly forming cavity. Were it not for the presence of these foreign cells, the earliest beginnings of the cavum mediale could not be easily determined from the material at hand, since this cavity differs in no other respect from a host of similar spaces found about the blood-vessels in the brain of this embryo, produced by too rapid interchange of fluids in the preparation for serial sections.

The further elaboration of the mesial cavity is furnished by embryo 423 (15.2 mm.), embryo 350 (15 mm.), and embryo 406 (16 mm.). In all of these specimens the tissue of the central nervous system is still intact in the region of the future lateral cavity. The cleft, which was barely demonstrable in No. 719 (15 mm.), has enlarged so that a complete separation of the nervous tissue has resulted. The vessel which was noted in the youngest embryo now lies exposed in the wall of the cavity, or even courses through it unsupported save for a few nerve-cells. Already the appearances of rupture of the nervous tissue have almost entirely disappeared and the protoplasmic strands which bridged the gap at its formation are wanting. Though not perfectly smooth in contour, as figure 2 illustrates, it has the appearance of being punched out of the section, so that healthy neuroblasts end abruptly at the boundary of the space. Occasionally one finds strands of cells bridging the mesial cavity at all periods of its existence. Such bridges are, then, comparatively large and are composed of many nerve-cells. The tissue making up the walls of the cavity is not in any sense a membrane, but appears to be composed of normal looking, undeveloped nerve-cells showing the same unbounded relation to one another as is found in the brain elsewhere. The edge of the space does not show the condensation of protoplasm such as is seen on the surface of the brain, where the cells form the external limiting membrane.

From the time of their first appearance, the cells contained in these cavities vary considerably in number as one compares different specimens. At times almost the entire mesial cavity is taken by macrophages which lie in close apposition to one another (fig. 8). For no apparent reason, the cell-content of the mesial cavity (and the same is true for the lateral cavity) varies considerably, but in general one finds a greater number of macrophages compared to the volume of the cavity in the mesial than in the lateral cavity.

Very quickly the mesial cavity reaches its maximum size. Thus in embryo 74 (16 mm.) the dimensions are roughly 195μ by 300μ by 416μ, but these dimensions are not constant in other specimens. There seems to be no relationship between the length of the embryo and the volume of the mesial cavity. Its method of disappearance seems to be by gradual contraction of its walls, so that there appears to be a tendency for the older specimens to have smaller mesial cavities. Thus in embryo 460 (21 mm.) the cavum mediale has vanished entirely from the left side and is but 96μ in its greatest dimension in the right corpus striatum. Neither the shape nor complexity of the space is characteristic. Usually, however, the cavity, with its smooth walls, assumes a spherical, ovoid, or lentiform shape. Many times diverticula extend from the main cavity, so that what appear to be multiple cavities in a single section, when traced through the series, turn out to communicate with one another. Figure 2 from embryo 350 shows such a condition. Finally there may be a duplication of these mesial cavities, so that two or more unconnected cavities may be found where normally only one appears. When this occurs each cavity is smaller than usual, but such a variation is not necessarily repeated on the opposite side of the brain. These cavities have but one distinguishing mark—namely, their position. As far as could be determined from series cut in the three planes, this space occupies a middle position in the striate body and is about as far from the cerebral ventricle as the surface of the brain. In figure 11 a geometrical projection gives its relation to the brain as well as to the lateral cavity. In the embryos of this collection no remnants of a mesial cavity appear when the length of 24 mm. has been exceeded.

THE CAVUM LATERALE CORPORIS STRIATI.

Farther laterally in the corpus striatum a second splitting of the nervous tissue makes its appearance soon after the medial one is evident. This space, which I have called the cavum laterale corporis striati, could not be made out in specimens 719, 350, 406, and 423. Embryo 144[1] (14 mm.) furnishes the earliest observed stage in the formation of the cavum laterale. An illustration (fig. 3) of the left side of this embryo gives a clear idea of its position in the brain. At the time of its appearance it occupies a deep position in the striate body just beneath the deeply stained ependymal zone. The separation of the nervous elements measures 270μ by 26μ, and may be traced through four sections—*i. e.*, 160μ of tissue. Its fellow on the other side of the brain has the same measurements. A drawing (fig. 4) of this less dense region brings out characters quite similar to those already described for the beginning mesial cavity. A narrow, elongated slit appears among the young nerve-cells which bridge over it with numerous thin filaments of protoplasm. In places the cell-body with its nucleus seems to be suspended midway between the diverging walls, as if undecided as to which it will follow. To the right, a small blood-vessel (*bv*) extends from one wall to the other. Moving among the strands of nervous tissue may be seen several large macrophages (*ma*) with their typical eccentric nuclei.

Like the cavum mediale, the cavum laterale reaches its full development very soon after its appearance. Its growth proceeds at the expense of the tissue lying between it and the surface of the brain, and usually halts only after a single layer of nerve-cells is interposed between it and the pia mater. All the transitional stages between the earliest evidences of a splitting of nervous tissue and such an appearance as is shown in the photomicrograph (fig. 5) have been found in the series of embryos here studied. The space does not always extend so close to the surface as this specimen would indicate. In every instance

[1]Measured from sections after mounting.

where good histological pictures were present there were no evidences of an anatomical opening under or through the pia mater. By studying the drawing (fig. 6) of a higher magnification the character of the walls and the behavior of the nervous tissue surrounding the cavity are more clearly made out. Roughly hour-glass in section, one finds the cavity spreading out just under the surface of the brain and having a narrow constriction where it adjoins the ependymal zone. Other embryos show an even more exaggerated narrowing than embryo 431 (18.5 mm.). Everywhere the contour is rough and broken by projecting masses of nerve-cells. Especially near the surface of the brain numerous delicate anastomosing processes of nerve-cells traverse the space. Five blood-vessels (*bv*) are included in this section, coursing from one wall to another. The characteristic phagocytic cells (*ma*) are present here in relatively larger numbers than in most of the lateral cavities. It is unusual to find macrophages so numerous as to form a morula-mass, except in the cavum mediale. Single cells are wandering among the protoplasmic strands along the edges of the cavity. A large amount of débris is present, floating about in the space, whether merely coagulated proteid or degenerated formed elements could not be determined. This cavity was the largest seen, measuring 500μ in depth from the brain surface and 350μ in average diameter.

Like the mesial, the lateral cavity varies considerably in shape, volume, and contents. The size does not increase *pari passu* with the growth of the embryo, except within the wide limits of its appearance and disappearance, both of which are remarkably sharp. In volume the lateral cavity is many times greater than the mesial, and owing to the irregularity of its walls has no characteristic shape. The diverticula are usually large and the lateral cavity is but seldom represented by several independent spaces. Here one usually finds delicate strands of nerve-cells stretching for a considerable distance across the cavity in a manner that suggests the growing embryonic nerve-cells on artificial media. This lends a roughened surface to the wall as contrasted with the smoother cavum mediale. Although the lateral cavities in embryo 431 (fig. 6) have many more macrophages per unit volume than the medial cavities of embryo 350 (fig. 2), in the main one finds but few cells in any one section of the lateral cavity.

For observing the relations of the cavities to one another a fortunate section through embryo 409 (16 mm.) was photographed with both low and high power magnification (figs. 7, 8, 9). The transverse section includes all four cavities, two on each side (fig. 7), and between the cavum mediale and laterale appears the dark mass of neuroblasts constituting the earliest nuclear anlagen in the striate body. Comparison of the magnified photomicrographs of the right mesial (fig. 8) and right lateral cavity (fig. 9) reveals the characteristics of both spaces as found in the study of the entire series of embryos. Most striking, perhaps, is the macrophage-content. In the mesial cavity almost the entire space is occupied by these phagocytes, while it is with difficulty that one makes out the five macrophages hidden among the delicate protoplasmic network making up the boundaries of the lateral space. The cavum laterale, as it lies just beneath the surface of the brain, presents a group of unconnected areas in cross-section, an appearance due to the processes sent out by the nerve-cells lying more or less within the cavity itself. Traced serially, they all communicate, forming a complex honeycombed system. In marked contrast to this is the smooth-walled cavum mediale, the rounded mesial wall of which is made up of embryonic nerve-cells arranged along the contour as regularly as if retained by a limiting membrane. The lateral boundary of this space is made up of a large engorged vessel (*bv*) which lies exposed in the cavity wall. It is very common to find a vessel standing out in relief in the mesial cavity, and rarely even passing through it.

THE DISAPPEARANCE OF THE CAVITIES.

The reoccupation of both cavities by nervous tissue and their consequent disappearance is apparently as rapid as are their appearance and growth. Embryo 460 (21 mm.) shows an extremely small cavity in the medial position on the right side and a complete absence on the left. In no instance could evidence of the mesial cavity be found after it had ceased to exist as a break in the nervous tissue, *i. e.*, in embryos greater than 24 mm. crown-rump length. An extremely interesting picture is furnished by embryo 453 (23 mm.), inasmuch as it constitutes a stage immediately following the replacement of nervous tissue in the cavum laterale. Close to the surface of this brain, where in younger stages one is wont to find the lateral cavities of the striate body, a considerable collection of macrophages lies among the nerve-cells. There is no longer any break in the nervous tissue, but, in a very circumscribed area, these phagocytes may be made out where the walls fused with one another. Large vacuolated cells are present in symmetrical positions on both sides of the brain and are undoubtedly beginning to migrate from the nervous tissue. The mesenchyme without the brain contains many of these same cells, which are present in greater numbers near the site of the former cavities. It is not improbable that the macrophages which we see here distributed among the nerve-cells would have crept out to join their brothers outside of the external limiting membrane.

Three specimens included in this list are worthy of notice, inasmuch as they constitute the extreme variations which have occurred. In the first, embryo 240, although its measurement is recorded as 20 mm., no sign of either space can be made out. The tissue is fairly well preserved and mounted. We are most likely dealing with a precocious or delayed development of the cavity. On the other hand, we may have a condition analogous to that obtaining for the pig. In this animal but two laboratory specimens, measuring 19 mm., showed an undoubted cavity in the corpus striatum (the mesial one) containing macrophages. Many serial sections of pig embryos from 10 mm. to 25 mm. were searched for evidences of either cavity, but in order to separate possible artifacts—which often occur in the central nervous system—from a true cavity, a typical vacuolated cell with eccentric nucleus was sought within the cleft. In all probability the existence of this cavity is of extremely short duration in this animal.

Embryos 128 (20 mm.) and 455 (24 mm.) showed a most remarkable degree of vacuolization of the striate body. The former embryo has a complicated cavity in the corpus striatum, which lies just under the ependymal zone between the mesial and lateral cavities. I have called this the cavum intermedium corporis striati, but it is evidently an anomaly. It is unconnected with either the medial or lateral cavity, which are well developed. The latter specimen shows a remarkable reduplication of the medial cavity. The region occupied by the medial group is very much larger, being extended laterally in the ependymal zone. There are so many small and independent spaces in the nervous tissue that it would be tedious to count them. In most of these cavities are found one or more macrophages, and their presence eliminates artifacts due to rapid dehydration.

DISCUSSION OF THE OCCURRENCE OF THESE CAVITIES.

One naturally inquires as to the rôle of these sudden breaks in the continuity of the nervous tissue coincident with the appearance of a foreign cell which proves to be a common element distributed in various parts of the embryonic body and young chorion, and which is in all respects the counterpart of the macrophage of the adult. Equally mysteriously, after persisting during the time in which the embryo grows 9 mm., there is just as abrupt an obliteration of these spaces and a complete disappearance of the phagocytic cells from the corpus striatum.

Before suggesting a probable reason for their existence, the possibility of an artifact must first be dismissed, since, in its early beginning, each cavity has the appearance of a shrinkage space. A large cavity having been observed occupying the center of the corpus striatum of a chick which has been incubated for 100½ hours, a specimen of similar age was carefully carried through graded alcohol in order to obviate as much shrinkage as possible. This chick was 121 hours old and measured 13 mm. in 40 per cent alcohol. It was fixed in modified Bouin's fluid, passed through 1 to 2 per cent grades of alcohol, and cut into 15μ sections in paraffin. Figure 10 is a photomicrograph from this specimen, and the degree of shrinkage may be judged by examining the retina. There is only the slightest tendency toward separation of the layers—and this is perhaps the most difficult organ to maintain perfectly without previously opening the eyeball to facilitate free interchange of fluids. Not one of the blood-vessels in the brain shows the slightest perivascular space, but each has a fully distended lumen. The medial cavity, illustrated on both sides, lies between the ependymal and nuclear zones. Contained within these complicated spaces are cells which are undoubtedly the macrophages, and which exist in very small numbers compared to the volume of the cavity. In all respects, except for the superficial position, the cavum corporis striati in the chick has the characteristics of the cavum laterale of the human embryo; *i. e.*, relatively few cells, roughened walls, and large, complicated lumen. There is no other cavity nearer the surface in either of the two specimens studied. No attempt has been made to follow the development in the chick, yet here is an excellent opportunity to compare the behavior of the macrophages in a vitally stained embryo.

Concerning the part played by these cavities, several possibilities have suggested themselves, but none are without objection. First, the spaces may be places where macrophages are formed during the short period of embryonic growth, just as the macrophage formation in the liver of the adult is limited to the endothelium. Glia cells have been described by Alzheimer (1) as forming macrophages ("Körnchenzellen") in the adult, and we may be dealing with such a transformation here. No such transition forms giving weight to this view were observed. If these spaces serve as foci of regeneration, then the size of the cavum laterale seems to be out of all proportion to the number of cells contained in it.

More likely we are dealing with an actual tissue destruction in the embryo of this early age. Both right cavities have been illustrated topographically (fig. 11). It will be noticed that this is the region about which a great shifting of tissue must take place to form the island of Reil and the temporal lobe. This mass movement might result in the destruction of earlier connections, and the macrophages are present simply to take away the débris formed by the rapid shifting of one portion of the brain over another. Two facts, however, are out of accord with this hypothesis; the formation of the Sylvian fissure has its inception in embryos of the third month and then progresses over a very long period; in other places, where extreme sliding of tissue, like the pontine formation, is present, one never finds this extreme grade of destruction.

A destruction due to other causes is possible; for example, the imperfect circulation of perivascular cerebro-spinal fluid which may be forming in larger quantities than can be absorbed. A dual source for cerebro-spinal fluid has been shown by Weed (**12**) as being derived from the choroid plexus and the nervous tissue via the perivascular spaces. Unpublished work, undertaken by him in the Anatomical Laboratory of the Johns Hopkins University, shows many interesting facts concerning the circulation of cerebro-spinal fluid in the pig embryo.

The various inconsistencies, as well as the lack of uniformity in structure, could be explained on the assumption of a slow accumulation of fluid about the vessels of the corpus striatum for a short time and its disappearance as soon as adequate pathways in the meninges are established. Such an hypothesis of an accumulation of fluid in the striate body gains support from many of these recorded findings. The invariable association of perforating blood-vessels with the cavities; the development of the spaces before the meningeal differentiation has proceeded far; the presence of coagulated protein-like contents; the bridging of the spaces by tissue strands resembling those of the adult perivascular canals—these are factors of possible consequence in this suggested origin. From this viewpoint, the accumulation of the intrinsic fluid of the nervous tissue resulted in the initial tissue destruction; further distention with more extensive tissue destruction and invasion of macrophages occurred; then, with a possible drainage outward of this fluid accumulation, the pressure was relieved and the space rapidly filled with the nervous tissue.

SUMMARY.

The observations here presented indicate that there occur in the corpus striatum of the human embryo between 15 and 20 mm. in length, two bilaterally symmetrical cavities. The presence in these cavities of cells morphologically similar to the macrophages of the adult and to the Hofbauer cells of the embryonic chorion argues strongly in favor of a functional significance. The lateral of these cavities is larger and less completely filled with macrophages than is the mesial. No satisfactory explanation of their presence can be definitely advanced.

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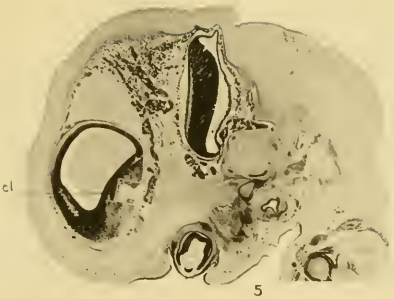

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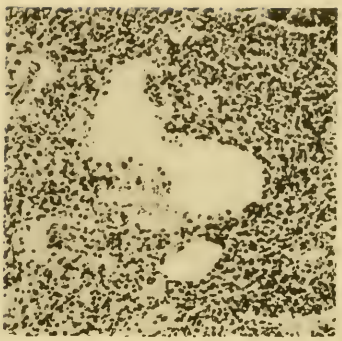

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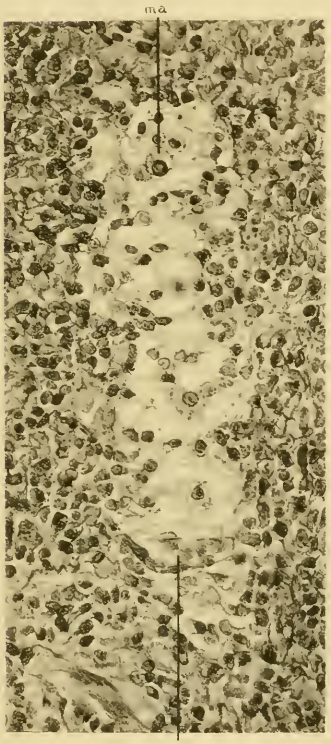

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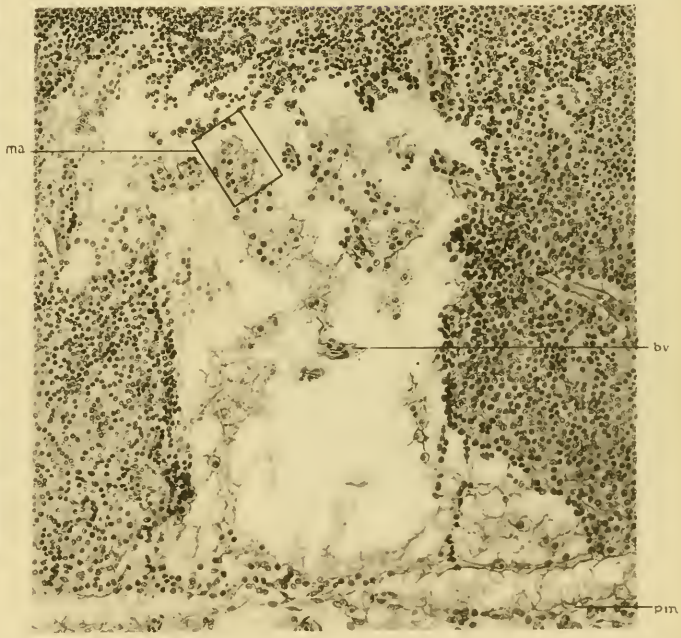

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1. Photomicrograph. Embryo 350 (*15 mm.*). Cross-section 75 - 1 - 5. × 8 The cavum mediale corporis striati (*c m*) appears in symmetrical positions on the two sides of the brain. That on the right side is given at a higher magnification in Figure 2.
2. Photomicrograph. Cavum mediale dextrum. × 144. The position is indicated in Figure 1.
3. Photomicrograph. Embryo 144 (*14 mm.*). Sagittal section 4 - 1 - 2. × 5. The earliest appearance of the cavum laterale sinistrum (*c l*) is indicated here and illustrated at a higher magnification in Figure 4.
4. Drawing of the cavum laterale corporis striati. × 500. Macrophages (*m a*) may be seen among the strands of protoplasm bridging the cavity. *b v*, blood-vessel The position of this drawing is indicated in Figure 3. (*Drawn by J. F. Didusch.*)
5. Photomicrograph. Embryo 431 (*18.5 mm.*). Sagittal section 12 - 1 - 1. × 7¼. The very large cavum laterale sinistrum (*c l*) is shown in its relation to the pia mater and the ventricle of the brain A more highly magnified drawing is given in Figure 6.
6. Drawing of the cavum laterale sinistrum. × 190 A single layer of nerve-cells separates the space from the pia mater (*p m*). Large numbers of macrophages (*m a*), a detailed drawing of which is given in Figure 12, are present. Blood-vessels (*b v*) traverse the cavity, surrounded by a few nerve-cells. The position of this drawing is indicated in Figure 5. (*Drawn by J. F. Didusch.*)

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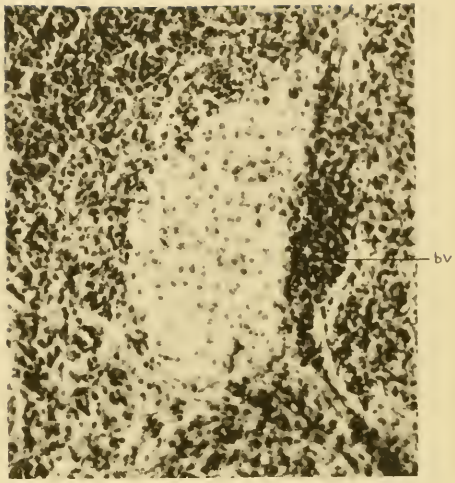

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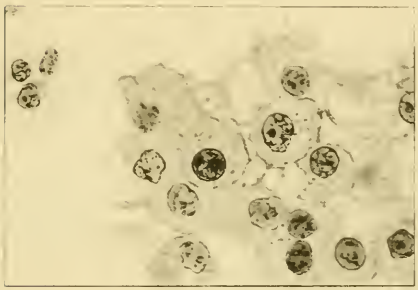

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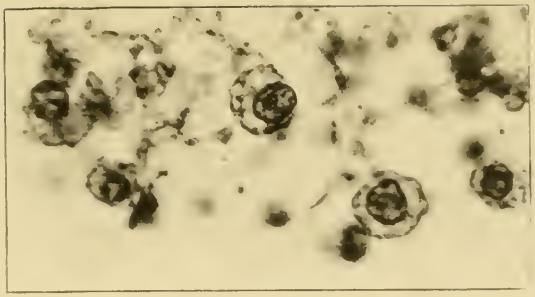
7. Photomicrograph. Embryo 409 (*16 mm.*). Cross-section 10 - 2 - 5. × 10. This figure illustrates the symmetrical positions occupied by the lateral (*c l*) and mesial (*c m*) cavities. Larger reproductions of them are shown in Figures 8 and 9.
8. Photomicrograph of the cavum mediale corporis striati. × 200. The smooth-walled space is packed with macrophages. An engorged blood-vessel (*b v*) forms its lateral boundary. The position of this illustration is indicated in Figure 7.
9. Photomicrograph of the cavum laterale corporis striati ×200. Some of the nerve-cells are growing across the cavity. The position is shown in Figure 7.
10. Photomicrograph of a section through the corpus striatum of a chick (121 hours incubation). × 7½. The cavities (*c s*) in the striate body are unusually large.
11. Geometrical projection of a model made at 50 diameters. Embryo 460 (*21 mm.*). ×6¼. The cavum laterale (*c l*) and cavum mediale (*c m*) are shown on the right side.
12. Macrophages indicated in Figure 6 × 1000. (*Drawn by J. F. Didusch.*)



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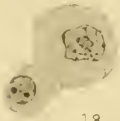

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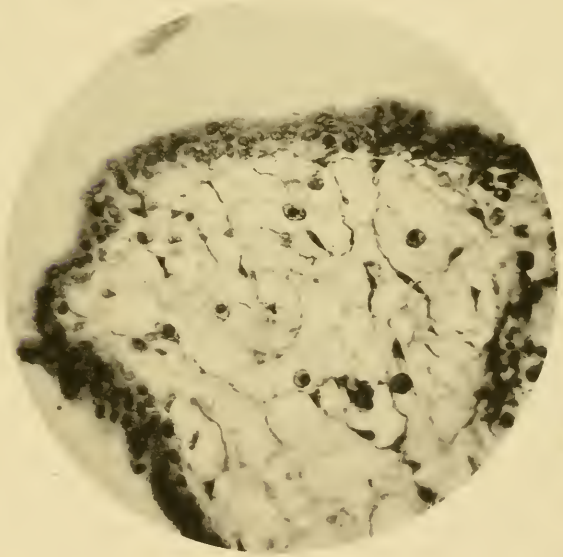

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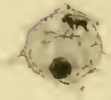

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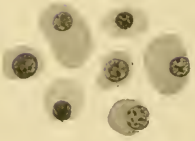

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13. Photomicrograph of macrophages in cavum mediale. × 1000.
14. Photomicrograph of chorionic villus of Embryo 350. × 410.
15-17. Macrophages from the chorionic villi. × 1000.
18-30. Macrophages from the cava corporis striati. × 1000.
31. Normal erythrocytes from a 15 mm. human embryo. × 1000.

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